Principles of Perinatal and Pediatric HIV/AIDS



Mamatha M Lala • Rashid H Merchant

Forewords
Hoosen Coovadia
Ishwar S Gilada
Janak K Maniar

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We dedicate this book to……

All the children who have lost their lives to the HIV epidemic and to those who continue to fight bravely in the face of this disease.......

In doing so, they not only inspire us to become better clinicians, but more importantly, teach us to smile and not to give up hope in spite of all adversities…..

In memory of Dr SM Merchant, who ignited the lamp of knowledge and inspired us to do the same and spread the light

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Foreword



I am extremely pleased to see this textbook appear in India where the epidemic of HIV in children has not attracted the attention it deserves. The comprehensive coverage in this textbook makes it a reliable guide to the management of HIV in children. Many health workers are intimidated by the prospect of caring for children with HIV and AIDS.

Dr Mamatha M Lala, Dr Rashid H Merchant and their wide range of authors have succeeded in providing sufficient details to reassure those who are familiar with pediatric HIV and introduce those unfamiliar with prevention and treatment of this grave disease. In many developing countries, the clinical and epidemiological burden of childhood HIV are often unappreciated, but the global burden and broad ramifications of this unprecedented epidemic demand recognition and are of universal concern.

HIV has introduced all of us, who care for children, wherever we may be, to profound issues about the future of infected children on lifelong drugs and the unpredictable long-term outcomes of those born in HIV positive households but who remain uninfected. Entire families are at risk when HIV emerges even in a single member. For clinicians, there is an enormous amount of work to be done to keep abreast with developments in this disease which is as much a social, economic and ethical challenge as it is, a biomedical disorder. This excellent textbook will meet the requirements of most who read through its pages.

The book is aimed at a rather wide audience and should be of value to practising physicians, pediatricians, obstetricians, family doctors, postgraduate students and many others who have the interests of children at heart. Globally in regions which are most affected by HIV, such as sub-Saharan Africa, there is an increasing recognition that medically trained doctors will not easily fill the gap in provision of health services created by the serious epidemics of the modern world. "Task-Shifting" allows other well-trained health professionals to deal with many problems conventionally dealt with by doctors; to such cadres of health workers, the chapters in this book will be extremely useful and may serve as a reference to simpler guides.

The dimensions of HIV are often misunderstood or ignored in countries in which it is not a major cause of infant and child death, but it is a major cause of child morbidity and death, mainly in HIV affected regions: In 2008, there were 2.1 million infected children under 15 years of age in the world; 430,000 of whom had become newly infected and 280,000 had died of AIDS related diseases in that year. Ninety-one percent of the new HIV infections in children were in sub-Saharan Africa. Ninety-five percent of these infections were probably due to mother-to-child-transmission. There was about 18 percent decrease in these numbers from 2001. It is estimated that about 200,000 new HIV infections in children had been prevented in the past 12 years. Of the total of 33.4 million persons infected with HIV in 2008, 15.7 million were women. HIV in pregnancy can worsen outcomes for both infants and mothers. There were an estimated one million HIV infected women who were pregnant in 2008 and who required PMTCT services. About 45 percent received these services in 2007. The antenatal months are pivotal in MTCT for the pregnant woman's and infant's health. Interventions to indirectly reduce vertical transmissions are well described in the book. Counseling on a range of issues is central to management. This includes advice on the use of antiretrovirals (ARVs) for either her own health or for PMTCT programs. By December 2008, coverage of adults and children for ARVs was 42 percent and more than 4 million adults and children were on treatment with ARVs; the number of children in need, receiving treatment was 275,700.

There are two key issues on treatment of children with HIV which are extensively addressed in this book: Early diagnosis and early treatment. Maternal antibodies obscure detection of HIV and other more elaborate tests are required. Knowledge of the mother's HIV status or her exposure to risky sexual encounters can alert the health professional to the need for testing both mother and infant. Shortages of skilled personnel and unavailability of technology very often account for the difficulties faced by clinicians in making a firm diagnosis of HIV in children.

Simpler and affordable tests for infant HIV diagnosis are an urgent need as clinical criteria for diagnosis are insensitive. Children have more rapidly advancing disease than do adults and delay in diagnosis result in high mortality rate. This is especially important for diagnosis of newborns and infants because, without appropriate ARV treatment, as many as a third of infected babies will die within a year, and most of these within a few months of birth. New WHO recommendations concerning treatment of children have recently been developed and provide practical guidance.

The richness of the text, the clear presentations from experts from all over the world—India, South Africa, the United Kingdom, the United States of America and Spain and the huge body of information within its 47 Chapters, ensures a wide readership and establishes this as a medical contribution which will be bought and consulted for many years to come.

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Foreword



It is my proud privilege to write a foreword for one of the first books on Pediatric HIV/AIDS— *Principles of Perinatal and Pediatric HIV/AIDS* from the Indian subcontinent. I have known Dr Rashid H Merchant for two decades and Dr Mamatha M Lala for more than a decade for their dedicated passion and single-minded pursuit, especially in the field of Pediatric HIV, wherein not many pediatricians dared to get involved even for fashion!

In a country like India where HIV is largely a heterosexual epidemic, Mother-to-Child Transmission (MTCT) of HIV-1 has a great significance afflicting thousands of children each year. Situation in sub-Saharan Africa is worse, where HIV prevalence is high and resources are scarce. Moved by this tragedy few researchers across Africa and Asia got involved in getting safe, efficient, innovative and inexpensive strategies that could reduce the risk of perinatal HIV transmission and increase uneventful survival of HIV positive children. In 1993, an NGO known as a torch-bearer in the fight against AIDS—the Peoples Health Organization, India (formerly Indian Health Organization) and Wadia Maternity Hospital in Mumbai had launched a self-funded low-cost project to look at these issues, when many countries had no affordable, easy-to-emulate options. Over the years, it became the country's (possibly the world's) first and longest running Prevention of Mother-to-Child Transmission (PMTCT) project. The project used a four pronged approach: Zidovudine to mothers in their pregnancy, Zidovudine to the infants, elective cesarean section for delivery and avoiding breastfeeding; simple innovations like group counseling and pool-testing were some by-products. A major offshoot of this project was emergence of India's first Pediatric HIV set-up as also emergence of these two authors as Pediatric HIV experts!

The fact that pediatric HIV and its repercussions will be with us for several years emphasizes the need for a sustainable response and the book on this topic is one such significant effort. This is indeed an elaborate and comprehensive textbook with as many as 47 Chapters dealing with Perinatal HIV and Pediatric HIV, contributed by a wholesome combination of several national and international experts, many belonging to centers of excellence in Africa, US and Europe. From Immunology, Virology, Natural History, Diagnosis, Pharmacotherapy to Clinical Manifestations and Management, all chapters have been eloquently dealt with, by the Who's Who in the respective fields. Chapters like Nutrition, Growth/ Development/ Puberty in HIV Positive Children, Malignancies and Immune Reconstitution Inflammatory Syndrome have been lucidly addressed. HIV-TB, HIV-Hepatitis and HIV-Malaria co-infections find a prominent place in the book. PMTCT has been elaborately dealt with and a guide is provided for care of HIV positive pregnant women. As children with HIV have started living longer, reaching adolescence and even marriageable age, the tackling of psychosocial issues related to growing up with HIV, which is the need of the hour, has been very sensitively portrayed. The ever-so-important areas of Antiretroviral Therapy, Toxicities, Adherence and Drug Resistance have been discussed in detail, as also the practical issues pertaining to Nursing Care of an HIV-positive Child in day-to-day life and Professional, Ethical and Legal issues have been very pragmatically presented.

The global HIV epidemic seems to be a permanent challenge to human existence, integrity and solidarity. Given the scale of suffering of children, given the proven effectiveness of several approaches in making them long-term survivors, and given the prospect of furthering other goals of the fight against HIV/AIDS, a sustained response makes practical sense. I have no doubt that this book—a collection of immense knowledge and experience from the global experts—is readily available to HIV care-givers and will certainly enhance the quality of care that the children will receive to further make their lives as meaningful as possible. It is a 'must read treatise' for postgraduates/physicians/obstetricians/primary medical practitioners/pediatricians as also all care providers for children with HIV. I wish the authors a grand success in this endeavor and hope each reader will admire the book, as much as me, if not more.

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Foreword



This comprehensive book on *Principles of Perinatal and Pediatric HIV/AIDS* has wide range of coverage of relevant topics compiled by both eminent national and international authors. There shall be need for periodical revision of the edition to update about rapidly changing views on HIV medicine. The scientific standard of topics is very satisfactory.

I recommend this book should be read by postgraduate medical students and by all health care providers involved in the management of pediatric AIDS and perinatal HIV intervention. I anticipate that this book shall succeed in sensitizing pediatricians at large, and increasing number of new children/adolescents with HIV shall be identified and managed appropriately. The text in the book should be made available on Internet for easy and instant access. I sincerely appreciate the grand efforts made by editors and contributors at large.

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Preface

The United Nations International Children's Emergency Fund (UNICEF) was founded in December 1946 in the wake of the World War II, when the international community recognized that children had special needs. Although the health of children has improved significantly over the last 60 years, much still remains to be done. The scourge of AIDS came upon the world in the last three decades. The developed world has succeeded in almost eliminating perinatal HIV transmission and has effectively given their already infected children a new lease of life. Health providers from developing nations need to shift emphasis towards priorities for improving child health care, and in doing so must pay special attention to preventing mother-to-child transmission of HIV and to the welfare of the HIV infected child. We believe that with adequate and appropriate support this challenge can and will be met in the future.

Pediatric HIV/AIDS is a vital discipline of modern pediatrics and in nearly three decades, researchers and clinicians have accumulated an abundance of scientific knowledge in this field. Unfortunately, little of this information is available in pediatric textbooks for clinical application. Although one of the major accomplishments in the management of HIV is the reduced incidence of mother-to-child transmission, even today a child is infected with HIV every minute, and about 1000 children die of AIDS everyday, claiming roughly half a million young lives every year. It is estimated that about 1300 infected children are born each day in Africa, 150 in India, and 1 in Europe or the US. Over the last two decades, therapeutic strategies for the treatment of pediatric patients with HIV have expanded dramatically from treatment with a single medication to combination therapy that includes up to five different classes of antiretroviral agents. The wealth of new information and experience available regarding rapidly emerging and changing pathogens, newer therapeutic agents and treatment regimens with renewed approaches to management, have made this specialized field more intricate and added to the complexity in management of what is now a chronic life-limiting illness. Effective management of the diverse needs of HIV infected infants, children, adolescents and their families requires attention to areas beyond antiretroviral therapy by a multidisciplinary team approach. It is important to remember that the long-term health of these vulnerable children depends on the sound judgment that we, as care providers, must exercise in their management.

This book, the first of its kind from the Indian subcontinent is directed to postgraduates, practicing pediatricians, physicians, obstetricians, general practitioners, non-governmental organizations, and all care providers of children with HIV, solely with a view to share knowledge for the benefit of patients, with no financial gains intended. It is aimed to provide a comprehensive, reliable, up-to-date reference focused on evidence-based, practical information that is required not only to prevent transmission of HIV to children, but also provide holistic care for the infected child.

Keeping in mind that children are our future, we are publishing this compilation of collective knowledge and experience of experts from across the globe. We hope that the information and insight it provides will take us one step closer to achieving our goal of enhancing the quality of care of HIV infected children and thereby provide them a chance for a better future.

Mamatha M Lala
Rashid H Merchant

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SECTION I

Basic Sciences

1.1

Immunologic Considerations in the Management of HIV Infected Children

Savita Pahwa

Introduction

Since the AIDS epidemic started in 1981, it has spread from a few high-risk groups to become a worldwide pandemic, with > 60 million people infected worldwide. In women aged 15 to 44 years, infection with HIV is a deadly foe—it is the highest cause of death globally in this population, accounting for 19 percent deaths[1] and is the major cause of HIV infection in children via mother-to-child-transmission (MTCT) of HIV. In non- breastfed infected infants, 25 to 30 percent infants have detectable provirus in their peripheral blood lymphocytes at birth, suggesting that they were infected *in utero*. In the remaining 70 to 75 percent, HIV-1 RNA or provirus is not detectable at birth, but becomes detectable by a week or two of age, suggesting intrapartum transmission of HIV-1. In breastfed populations, approximately 15 percent of infection are thought to occur *in utero*, 65 to 70 percent during delivery, and 15 to 20 percent are thought to occur postpartum through breastfeeding.

The first and greatest milestone in the history of pediatric HIV infection has been the ability to interrupt MTCT with antiretroviral drugs given to the mother and infant or to infant alone as post-exposure prophylaxis. Maternal plasma HIV-1 load is the strongest predictor of MTCT, and the risk of transmission increases with increasing maternal plasma HIV-1 load. Although MTCT can occur at any maternal viral load, it is rare (<1 percent) when maternal plasma HIV-1 RNA is <1000 copies/ml. In the developed world, MTCT rates reduced to approximately 1 to 2 percent since the advent of highly active antiretroviral (HAART) therapy, as opposed to 25 to 45 percent without antiretroviral (ARV) intervention to suppress maternal viremia. HAART for all women is fast becoming the accepted form of management of HIV infection in pregnancy in USA and Europe. The fact that >1,000 infants are still infected daily in the post-HAART era is a sad reminder that MTCT interventions is not used worldwide.[2] From the global viewpoint, adoption of universal provision of fully suppressive ARV regimens to all HIV-1 infected women through pregnancy, delivery, and the entire breastfeeding period would go a long way in eliminating perinatal HIV transmission.

Another major milestone is the demonstration of the profound impact on the morbidity and mortality of HIV/AIDS with early treatment of an infected infant. Although HIV therapy has not yet realized its ultimate goal of HIV eradication, the preservation and restoration of the immune system through proper ARV implementation offers a chance for a healthy life in newly diagnosed HIV infected infants and to make an impact on lives of chronically infected children; failure to treat or suboptimal therapies robs HIV infected children of this chance.

Infants and children differ from adults in terms of immune responses which is underdeveloped, but they have the advantage of a functional thymus that gives them better capability of immune reconstitution. An understanding of the immune system in children and the impact of HIV will help caregivers understand the basis of the immune deficiency that accompanies HIV, and adopt measures to prevent devastating consequences.

Overview of HIV Structure and Life Cycle and Host Restriction Factors

The HIV-1 genome is composed of approximately 9 kb of RNA, which consists of nine different genes encoding 15 proteins.[3] Two copies of the single-stranded genome are packaged in the virus particle along with additional enzymes and accessory proteins. Three genes, Gag (group specific antigen), Pol (polymerase) and Env (envelope) polyproteins, are proteolytically cleaved into individual structural proteins and enzymes. Gag is cleaved into four structural proteins: matrix, capsid, nucleocapsid and p6, while Env is cleaved into surface gp120 and trans

membrane gp41. Pol cleavage produces the enzymes protease, reverse transcriptase and integrase, which are encapsulated in the virus particle. In addition, HIV also has six accessory and regulatory proteins: nef, vif, vpr, vpu, rev, and tat which play key roles in the viral replication cycle. Infection of target cells is initiated by the binding of the gp120 envelope molecules on the viral surface to the CD4 receptor and to CCR5, a chemokine coreceptor expressed on T cells, macrophages and dendritic cells. Another chemokine coreceptor CXCR4 is usually utilized by HIV-1 in advanced stages of infection when the virus changes its tropism or becomes dual tropic and further expands its targets. It has been proposed that the envelope gp120 also binds to integrin 4 alpha 7, a transmembrane protein on CD4+T cells. This attachment mediates the migration of CD4 + T cells to the lymphoid tissue in the gastrointestinal tract and activates the expression LFA-1 (Lymphocyte Function Associated Antigen-1) which in turns mediates the formation of virological synapses thereby promoting the dissemination of HIV-1.[4]

The binding of gp120 with the CD4 receptor initiates a conformational change in the virus envelope with exposure of hidden envelope epitopes in the transmembrane region and set off a series of steps resulting in ultimate fusion of the virus and host membranes and injection of the viral contents into the target cells. Viral replication and transcription are initiated by reverse transcriptase, which copies the single stranded viral RNA into its double stranded complementary proviral DNA.[5] This step is highly error prone and gives rise to a high number of mutations or quasispecies that enable the virus to escape recognition by the cellular immune system.[6] Upon cellular activation (by antigens, cytokines, mitogens and to a certain extent even gp120 itself), the complementary DNA is transported into the nucleus where viral integrase incorporates it into the host cell DNA. Transcription of the DNA into viral mRNA and genomic RNA is facilitated by NFkB. The viral mRNA is translated into polyproteins, which are then cleaved by viral and cellular proteases and assembled into new virions which are shed off and bind to new target cells.[5]

Several viral proteins play important roles in crippling host defences. Immune defects in HIV infection have been attributed to the direct effects of infection of CD4 cells and to the indirect effects mediated by viral proteins. For example, Nef downregulates the expression of CD4 and Major Histocompatibility Complex (MHC, also called Human leukocyte antigen – HLA) Class I molecules, and interferes with T cells activation, thereby providing an escape mechanism from virus-specific CD8 cytotoxic T lymphocytes (CTL). HIV envelope glycoprotein has been shown to have immune suppressive properties and drives apoptosis of uninfected and infected cells.

Host restriction factors and interaction with viral factors: Host factors which restrict HIV replication include APOBEC3G, Trim 5a, CD317 (tetherin), others. The virus in turn counteracts host restriction factors via accessory proteins (vif, Vpu, Nef, Vpr). It employs multiple strategies for immune evasion to disarm the immune system and depends upon the expression of a large set of host cellular genes for effective replication.[7, 8] Host restriction factor APOBEC3G (apolipoprotein B editing enzyme catalytic polypeptide-like 3G), acts on HIV-1 to prevent the synthesis of proviral DNA. This is counteracted by the viral vif. By binding to APOBEC3G, vif inhibits its function and therefore promotes viral replication. A cytoplasmic body called Trim 5a binds to HIV Gag capsid protein and accelerates viral uncoating, thus inhibiting HIV replication before the reverse transcription step. In resting CD4+ T cells, NFkB can be inhibited by a cellular protein Murr1, the activity of which correlates with the inhibition of HIV replication in quiescent CD4+ T cells. Tetherin prevents the release of newly synthesized virus from the infected cell surface by tethering or anchoring it and is inhibited by viral Vpu. Discovery of host restriction factors is a major area of research as it has the potential to uncover new targets for therapy.

Viral Dynamics, HIV Disease Progression

Following inoculation of HIV into the host via the mucosal route, there is an initial period lasting approximately 10 days, termed the Eclipse phase during which the virus is undetectable in peripheral blood.[9] In this time, the virus traverses through the submucosa, spreads into draining lymph nodes through infection of activated CD4+CCR5+ cells and establishes the viral reservoirs. The burst of plasma viremia that characterizes the acute phase of HIV infection (see below) is a reflection of rapid viral disseminated to lymphoid tissues, particularly GALT, which has high numbers of CD4+ CCR5+ memory like T cells. Approximately 80 percent of the gut CD4 T cells are rapidly depleted, partially by direct infection of target cells (approximately 20%) and indirectly by activation induced cell death of uninfected cells (approximately 60 %).

Less is known about early events in perinatal HIV infection, as the initial course of HIV infection following MTCT has not been charted out. It is not known if in the HIV infected neonate, the gut is the initial organ of attack with destruction of immune cells. If the initial course of infection bears similarity to the mucosal inoculation with an initial eclipse phase prior to and spread described above, it would explain the fact that *in-utero* infections can be detected in peripheral blood virologic assays at the time of birth, whereas intrapartum infections cannot be reliably detected prior to 2 weeks after birth.

The initial burst of plasma viremia during the acute phase of infection in adults lasts 1 to 2 months following inoculation and is followed by a decrease in viral load with the 100 to 1000-fold reduction in plasma HIV-1 RNA levels to a set-point and subsequent steady state plasma HIV-1 RNA levels within 6 to 12 months of primary infection. In children peak viremia is higher and the acute phase lasts longer than in adults. Plasma HIV-1 RNA levels of 10^5 to 10^7 copies per milliliter have been documented in vertically-infected infants over the first 1 to 2 months of life, and high plasma viral load persists over the first 1 to 2 years of life. Plasma VL in infants decreases gradually over the first 1 to 2 years of life, to about 30,000 copies by the age of 2 years.[10] Continued declines in plasma HIV-1 RNA levels (mean 0.2 to 0.3 log decline per year) have been documented through 6 years of age.[11]

Decline in viral load is attributed to antiviral effects of the immune system, particularly cytotoxic T cells. The prolonged elevation of plasma HIV-1 RNA levels may be related to the kinetics of viral replication, the size of the pool of host cells that are permissive to viral replication, or deficient virus-specific immune responses. A large and renewable pool of permissive host cells may contribute to persistently high plasma HIV-1 RNA levels in infancy and early childhood, although it is unclear whether these differences in peripheral viral load affect disease progression. Early in infection, a reservoir of "latently" infected cells is established in adults and perinatally infected infants, consisting of replication-competent virus in a pool of long-lived resting memory lymphocytes, and perhaps in other cells as well. Although the size of the pool is small, it may serve as a source of lifelong persistence of infection, and pose a barrier to eradication of infection despite potent HAART.[12]

HIV and the Immune System

General Considerations

The major cellular compartments of the immune system are made up of cells of adaptive immunity, namely T and B lymphocytes, and innate immunity, i.e. monocyte/macrophages, natural killer (NK) cells, dendritic cells and granulocytes. Among T cells, CD4 and CD8 T cells constitute the major subsets. Each cell type relies on a series of interactions between receptors on the cells and extracellular ligands which lead to a cascade of second messenger systems within the cell including transcriptional activation, and synthesis and secretion of a variety of factors, including cytokines and chemokines. In turn, cytokines and chemokines trigger and regulate cellular responses. Antigen presenting cells (including monocytes and dendritic cells) help in antigen uptake and presenting the antigen in appropriate format (peptide or protein) to CD4 and CD8 T cells and B cells via MHC Class 1 or Class II molecules. These cells particularly granulocytes and monocytes can also clear bacterial pathogens by phagocytosis and bactericidal activity. Some of the immunologic components are immature at birth and their development continues after birth. There are normal age-related changes in lymphocyte subpopulations. CD4 T lymphocyte counts are highest at birth and in the neonatal period and decrease to adult values by 6 to 7 years of age. The CD4:CD8 ratio in young children can be three times the CD4:CD8 ratio in adolescents or adults. Thus, T cell values in pathologic situations such as HIV infection should be evaluated in relation to age-associated normal values.

The major target cell for HIV infection is the CD4-T helper cell, which is considered central to the orchestration of the immune responses. They form the main target of infection by HIV, through the binding of HIV envelope to receptors CD4 and a chemokine receptor, usually CCR5, and later in disease also to CXCR4, with widening viral tropism. As with any other infectious process, the rate of progression of HIV depends on complex interactions between the virus, the host, and the environment. Although protective immune responses are likely to play an important role in controlling disease progression, immune markers of protection are not yet well defined. Major components of the immune system that are thought to play a role in HIV specific immunity are HIV specific cytotoxic CD8 T cells, CD4 helper cells, and neutralizing antibody. In an attempt to dissect the immune response to HIV, considerable attention has been given to the relatively few individuals (1 to 2%) who remain healthy for prolonged periods after being infected (long-term non progressors) and to those who remain uninfected despite repeated exposure to HIV. In addition, investigators have carefully analyzed the immunologic changes following acute infection with HIV. In most individuals HIV infection compromises general immune competence as well as the development of HIV specific immunity. HIV activates cellular responses that are deleterious to the host and lead to qualitative and quantitative T cell deficiency involving CD4 and CD8 T cells.

Thymic Function in HIV Infected Children

The maturation of T cells occurs in the thymus—an organ that plays a pivotal role throughout life in generating T cells of different antigenic specificities so that all possible invaders can be confronted and dealt with appropriately. The thymus, which is largest at birth and during the first few months of life, involutes with age. By adolescence, the thymus is greatly diminished in size, although recent studies indicate that thymic remnants are functionally active well into the fifth and sixth decade of adulthood. In the context of HIV, thymocytes might be particularly important substrates in infants. Relative lymphocytosis,

thymopoiesis and an increased CD4+ T cell pool size could be a contributing factor to the high virus burden in infancy.

The inability to control viremia during acute infection could also expose the thymus to HIV-1 mediated destruction at a time of active thymopoiesis. Pediatric thymic dysfunction as a result of *in utero* infection may account for the rapid disease progression observed in 20 to 30 percent of HIV-1 infected children. In such infants, a pattern of lymphocyte depletion develops that resembles a pattern observed in congenital thymic deficiency. HIV-1 may directly kill thymocytes and thymic DCs required for normal thymocyte development and can damage thymic epithelial cells required for normal thymopoiesis and thymocyte signaling. HIV-1 RNA expressing cells are found both within the thymic perivascular and true thymic epithelial spaces during early and late HIV-1 infection.

Thymocyte depletion, loss of corticomedullary demarcation and the development of thymic medullary B cell follicles has been noted to occur in untreated HIV infection. These changes are associated with presence of HIV-1 structural proteins in thymocytes and evidence of viral replication most commonly with CXCR4-utilizing isolates of HIV-1, which are tropic for CXCR4+CD3⁻ CD4+CD8⁻ intrathymic T progenitor cells. In contrast, CCR5-utilizing isolates infect intrathymic myeloid and thymocyte subpopulations that are more mature, and result in thymocyte depletion after long periods of time. Indirect evidence of thymic involvement includes decreased circulating CD4+ and CD8+ naïve T cells and cells bearing T cell receptor rearrangement excision circles (TRECs) (markers of recent thymic emigrants) during disease progression. Signs of thymopoiesis appear to return after effective HAART[13,14] particularly if the subject is younger and does not have evidence of thymic involution.

T Cells and HIV Infection

T cells play a key role in protection from viral infections. Based on their surface phenotype,[15] human T cells can be characterized as naïve (N), central memory (CM) which predominate in lymph nodes, effector memory (EM) which predominate in tissues and blood stream, effector (E) and terminal effector (TE) cells which are directed at the infected target cells. While the differentiation pathways of naïve to memory T cells are debatable, there is agreement that memory CD8+ T cells differentiate to become effector cells. T cell responses are commonly represented as the frequency of antigen-specific T cells or the expression of a specific effector function. Important methodological advances in flow cytometry have made it possible to simultaneously characterize multiple functions, enabling a broad assessment of the frequency, magnitude, phenotype and functional capacity of T cells on a single cell basis. Polyfunctional T cells (PFT) in which single cells manifest 3-5 antigen specific functions including capacity to secrete key cytokines, are considered to be crucial in mediating antigen-specific responses against inciting pathogens including HIV and for vaccine induced immunity.[16] Virologic control against HIV has been shown to correlate with proliferation of memory cells and their differentiation into effector cytotoxic CD8 T cells expressing perforin[17] with preservation of CD4 T cells. The dysfunctional immune system leads to a large number of CD4+ T cells undergoing apoptosis before expanding into effector T cells. CD8+ T cells do not seem to follow the exact same fate with a large number of antigen specific CTLs undergoing expansion and differentiation into pre-terminally differentiated effector cells.

Both CD4+ and CD8+ T central memory cells are located in the secondary lymphoid organs and have little or no immediate effector function. They proliferate and differentiate into effector cells when stimulated by cognate antigens. T_{EM} cells on the other hand are located at the periphery enabling them to exert immediate effector function. The failure of the T cell directed HIV vaccine in the STEP trial emphasizes the need for continued investigations of the breadth, specificity and quality of vaccine-induced T cell responses to understand the constituents of a protective response. Importantly, there is still no consensus on what is the best adaptive T cell immune correlate of protection, but most agree that cytotoxic T cells form an important component of host defense against HIV.

Cytotoxic T Cells

Cytotoxic T cells have been shown to play an important role in host defenses against HIV by potentially eliminating infected cells and controlling the extent of infection. Cytotoxic T cells "kill" the infected target cells in a MHC-restricted manner (i.e. MHC compatibility between target cells and effector cells is required), by mechanisms that require cell-to-cell contact and exocytosis of secretory molecules, such as perforin and granzyme, as well as engagement of death receptors (Fas) on target cells to induce apoptosis. Cytotoxic CD8+ T cell activation is dependent of interaction between antigenic peptides on the MHC Class I molecules and the CD8+ TCR, cytokynes secreted by Th cells and costimulatory molecules. The cell surface expression of 107a on CD8+ T cells is positively associated with the release of perforin/granzyme molecules.

In the period of acute infection following HIV transmission, HIV specific CTL precursors can be detected in the host before seroconversion, with the peak in CTL activity coinciding with the decrease of the initially very high viral load to the lower levels seen during chronic

infection. These observations imply that CTL are critical for initial antiviral activity during acute phase of HIV infection, resulting in considerable but variable lowering of virus load to a set point, but the CTL generated are unable to eradicate the virus. Associations between strong CTL responses and both delayed disease progression and low viral loads have been noted. Importantly, progression to AIDS is marked by increased viral replication accompanied by the loss of the HIV specific CTL response.

The deficiency of CTL responses in infancy have been attributed to immaturity of the immune system. Interestingly, young HIV-1 and cytomegalovirus (CMV) co-infected infants lacking HIV specific CD8+ T cells have been shown to manifest CMV– specific CD8+ T cells[18] implying that young infants are capable of generating virus-specific CD8+ T cells. The paucity of detectable HIV-1 specific CD8+ T cell responses represents a selective defect in the generation or maintenance of HIV-1 specific CD8+ T cells. Possible mechanism for defective CTL infancy include the presence of high titer of passively-acquired maternal antibodies at the time of acquisition of HIV-1 infection, or early depletion of HIV-1 specific CD4+T cell help required for the generation and maintenance of HIV-1 specific CD8+ T cell responses.

Using flow cytometry, antigen specific CD8 T cells can be identified based on their ability to bind tetramers carrying relevant HIV peptides in a class 1 restricted manner. Although a majority of patients with established HIV infection have epitope-specific CD8+ T cells demonstrated by their ability to bind HIV peptide loaded tetramers, the numbers of antigen-specific cells often do not show a correlation with virus load, thereby raising the question of whether these are functional. A study performed in children and adolescents with chronic, perinatally acquired HIV infection demonstrated that HIV Gag- and HIV Pol-specific cells were detectable in most patients by tetramer binding, but only a small percentage expressed perforin. Moreover, HIV specific cells expressed CD27, an antigen reported to be lost in the transition from memory to effector phase,[19] which suggested failure of maturation of CD8+ T cells to effector cells with cytolytic capabilities. Ability to generate antigen specific polyfunctional CD8+ T cells that express at least 3 cytokines (IFN-g, IL-2, TNF-a or MIP-1b) plus the degranulation marker CD107a is considered to be the signature "protective" CD8 T cell response.

Population-based studies suggest that the efficacy of a CD8+ T cells response may depend in part upon the HIV protein from which the targeted epitope is derived– in particular, CTL population targeting Gag epitopes to be associated with superior viral containment.[20] Defective Gag-specific CD8+ T cells responses during early in the infancy, especially among children younger than 24 months have been reported.[21] Both total and Gag-specific T cell frequency correlated inversely with viral load after correlation with age, and an inappropriate response of CD8+ T cells to Gag may contribute to the inability of young infants to limit replication of HIV.

HIV has evolved multiple mechanisms of escape from the host CTL. HIV gene products particularly Nef downregulates the major histocompatibility complex (MHC) class I expression in infected cells, thereby preventing CD8+ T cells to efficiently eliminate HIV infected target cells. Other means by which HIV can escape CD8+ T cell attack include sequestration of infected cells in the central nervous system with limited T cell access. All latently infected cells are invisible to detection. HIV diversity is fueled by high rates of error-prone viral replication, and is a key player in resulting failure of host immunity. Development of escape mutations in HIV under immunologic pressure of CTL is another feature of HIV-1 infection that is associated with failure of CTL to eliminate HIV. Longitudinal studies of individual patients, matching dominant CD8+ T cell responses with viral changes in amino-acid sequence, have identified clear cases where a single change has abrogated presentation by the class I HLA molecules and these mutated viruses become dominant quasispecies. Escape from one CD8+ T cell population is followed by a new CD8+ T cell response directed against new epitope but the same pattern of escape mutations leads to ineffective cytotoxic responses. These infected cells escape lysis and propagate the mutant virus. The rate of mutation is influenced by the balance between the strength of killing and the level of viral replication, and may be also influenced by impairment of CD8+ T cell function.

Host genetic diversity, including the extreme polymorphism of HLA, in turn, is one of the means to combat the spread of pathogens through populations. The composition of the HLA alleles, play a role in determining the strength of CTL responses and influence the ability of the virus to develop escape mutations, and consequently the virus load. Examples of protective alleles include HLA-B*27 and HLA-B*57, whereas HLAB*18 and B*5802 are nonprotective. The specificity of the CD8+ T cell response, particularly the response to Gag, is associated with low viral loads in HIV infection.[21] Although immune control is undermined by the selection of viral mutations that prevent recognition by the CD8+ T cells, evasion of Gag-specific responses mediated by protective class I HLA-B alleles typically brings a reduction in viral replicative capacity, facilitating subsequent immune control of HIV.[22] This is important in the context of mother-to-child HIV transmission when the child lacking an immune response or protective alleles nevertheless benefits at least early in the disease due to transmission of an attenuated virus as a consequence of maternal

Gag-specific CD8+ T cell responses that have altered RC of the virus.

The more usual scenario is that the mother does not carry protective alleles and as maternal risk of transmitting HIV to her offspring is usually related to viral load, it is probable that the mother has nonprotective alleles, such as HLA-B*18 and -B*5802. At the least, a child will share 3 of the 6 HLA-A, HLA-B and HLA-C class I molecules with his or her mother. MTCT involves transmission of virus between genetically similar individuals. There are two distinct ways by which her infected baby would manifest more rapid progression. First, because infected children share 50 percent or more of their HLA alleles with the transmitting mother, the chance that he/she carries protective HLA alleles is vastly decreased. Thus, infected children in general carry fewer protective HLA alleles and more nonprotective HLA alleles. Second, even if a child has a protective allele, such as HLA-B*27, this allele will offer protection only if the maternally transmitted virus is not preadapted and thus does not carry escape mutations within the key Gag epitopes that are required for presentation by the protective allele. The relevance of maternal HLA-mediated selection pressure on virus transmitted from mother to child is evident in the detailed study of four HIV infected mother-child pairs who all had a B*27 allele.[23] It demonstrated that the B*27 allele was only protective if it was inherited from the father. When the same allele was inherited from the mother, the children exhibited mutations in viral epitopes and defective CTL response. Children with greater similarity to their mothers with respect to their HLA genes had faster disease progression.[24]

CD4+ T cell Subsets, Immune Activation and Mechanism of CD4 Depletion

CD4+ T lymphocytes (T helper- Th) are pivotal to the immune system as they coordinate the functioning of the adaptive and cellular immune response while CTL are responsible for the killing of infected cells. In contrast to CD8+ T cells that are activated by cells expressing MHC Class I molecules, CD4+ T cells are activated by professional antigen presenting cells (APCs that comprise B cells, macrophages and DCs) that bear antigenic peptides presented by MHC Class II molecules. In fact, trafficking of HIV bearing DCs to activated CD4+ T cells in the lymph nodes allows for the dissemination and establishment of HIV in the host cells. CD4 T cells provide important helper function to T cells including CD8 T cells and B cells. Once activated naïve CD4+ T cells differentiate into effector T cells (Th1, Th2 or Th17) or into regulatory T cells (Tregs), during this differentiation process, coordinate genes are activated that determine whether the effector cells differentiate into central memory (T_{CM}) or effector memory (T_{EM}) cells.[15] Cytokines secreted by the effector Tcells establish an autocrine positive feedback loop resulting in the clonal expansion of large numbers of antigen-specific T cells to generate effector CD4+ T cells which perform their function either in the blood or lymph nodes.

Th1 cells are considered to be critical for orchestrating a variety of immune responses through cell/cell contact and through secretion of cytokines. Th1 cells mainly produce IL-2, TNF-a and INF-g cytokines and direct their activity to bacterial and viral infections. Th2 cells secrete IL-4, IL-5, IL-6 and IL-13 and are involved in providing B cell help in promoting T-dependent antibody production and eliminate parasites and are implicated in allergic responses. Th-17 cells play an important function in the gut, with IL-17 secretion acting to promote neutrophils for protection against intestinal bacterial pathogens. Recently established Tfh cells is another CD4 subset which is the main producer of IL-21, which has multiple cellular targets including B and T cells.[25] TfH cells are also important for helping B cell maturation in germinal follicules through secretion of IL-21.

The past few years have also seen much coverage of Tregs in HIV infection. T reg cells can suppress immune responses and are believed to be important in dampening immune responses and preventing autoimmunity and inflammation. Two characteristics of Tregs have emerged: they have a inhibitory effect on effector T cells mediating antiviral activity; in particular they inhibit the proliferative response to HIV antigens but also reduce the level on immune activation, which could have beneficial effects for HIV-1 immunity.[26] There is also evidence that Tregs skew the CD4+ T cell response away from a Th1 to a Th2 type response. Their role in HIV pathogenesis is controversial, and a balanced Treg activity is desirable. Overactivity can suppress protective immune responses, but their deficiency can lead exaggerated immune responses which can be deleterious in many circumstances. The current consensus to identify Tregs is the presence of CD4+, $CD25_{high}$, FoxP3+ and $CD127_{low}$.[26] Tregs are high in cord blood and early infancy and have been implicated in suppressing neonatal immunity to various pathogens.

It has been well documented that CD4+ T cells secreting IFN-g only represent a skewed cytokine response caused by constant exposure to antigen. CD4+ T cells producing both INF-g and IL-2 were negatively associated with viral load, and low frequencies of IL-2 producing CD4+ T cells were associated with a reduction in their proliferative capacity.[27] Taken together, it was concluded that HIV-1-specific CD4+ T cells in untreated patients with progressive disease have a cytokine secreting profile skewed to producing INF-g alone that render them relatively nonfunctional. CD4+ T cell defects during disease progression include a decrease in the proportion of quiescent naïve CD45RA+CD62L+ T cells and an

increase in the proportion of activated memory phenotype (CD45R0+). At the same time the T cell receptor repertoire is restricted.[28] HIV impairs polyfunctional CD4 T cell responses against BCG in BCG vaccinated HIV infected infants as determined by flow cytometry, based on coexpression of type I cytokines. Qualitative deficiencies were present in BCG–specific CD4 T cell responses of HIV infected as compared to HIV exposed uninfected and HIV negative age matched controls.[29]

It is of interest that most circulating CD4+ T cells in early childhood are of the naïve phenotype. Naïve CD4+ T cells reportedly have lower cell surface levels of CCR5 and are less permissive for HIV-1 replication than memory CD4+ T cells. Normally, as a result of exposure to antigens, cells with the memory phenotype expand gradually after birth with the functional role of T cells being the provision of a defense system against intracellular pathogens such as mycobacteria, fungi, and most viruses. Progressive loss of CD4 T cells is a hallmark of HIV infection. The obliteration of memory CD4+ T cells severely impacts on the ability of the adaptive immune system to ward off pathogens it had previously encountered, thereby permitting the establishment of opportunistic infections that characterize HIV/AIDS infections. Severe deficiencies in the T cell system result in failure to thrive and susceptibility to opportunistic infections. CD4 nadir at initiation of antiretroviral therapy influences immune recovery.

a. ***The mechanisms of CD4 T cell depletion:*** This topic has been an area of intense research. A number of hypotheses have been developed to account for CD4+ T cell depletion. An important point that has been well established is that CD4 depletion in chronic HIV infection is caused not only as a result of direct killing of infected cells by the virus or CTL but also by bystander cell death of uninfected T cells. Quantitative estimates indicate the normal young adult possess approximately $2X10^{11}$ mature CD4+ T cells. This number is halved by the time the CD4+ T cell count decreases to 200 cells/μL. Among the mechanisms of cell death the first and foremost is attributed to activation induced cell death or apoptosis as a result of aberrant immune activation. This topic is discussed below. Other factors include impairment of thymic function as described in the earlier section. Thymocyte depletion, with decrease in TREC signify impaired production of progenitor cells. Signs of thymopoiesis appear to return after effective HAART,[13,14] particularly if the subject is younger and does not have evidence of thymic involution. Sequestration of CD4 cells in lymph nodes due to increased adhesion molecules (VCAM-1, ICAM-1), has also been proposed as another factor that depletes circulating CD4 T cells and promotes CD8 dominance in peripheral blood.

b. ***Aberrant Immune Activation:*** Aberrant immune activation is a hallmark of HIV infection, resulting in expression of activation markers on T cells (DR, CD38, CD95), secretion of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-a and increased lymphocyte apoptosis.

   The exact cause of increased immune activation is not confirmed. Two major sources of immune activation include; first, the HIV and its proteins and second, products of gut microbial translocation due to damage inflicted on the gut during acute infection. HIV and its proteins drive aberrant immune activation by stimulation of innate immune system, by direct and indirect stimulation of T and B cells and by inhibiting immunoregulatory mechanisms, e.g. impairment of T-regulatory cells.[30]

   Bacterial products resulting from microbial translocation drive immune activation of innate and adaptive immune system. HIV induced gut damage in acute infection leads to microbial translocation in chronic HIV infected state.[31] The gut associated lymphoid tissue (GALT) is the site of considerable virus replication in primary HIV-1 and Simian immunodeficiency virus (SIV) infection and leads to depletion of CCR5+CD4+ T cells by direct infection, apoptosis or direct killing by CTLs, and establishes a reservoir of HIV-1 that cannot be easily eradicated by HAART. CD4+ Th17 cells are also the target of cell death in the GALT and they are found in low frequencies in acute SIV and in HIV infection and correlate negatively with plasma virus level. The compromised immune integrity in the GALT allows for the translocation of microbial products from the gastrointestinal tract, which can account for the chronic state of heightened immune activation observed in HIV-1 infection.[31] Data in adults and children suggest that this is a mechanism of ongoing immune activation. Immune activation as a marker of disease progression is valid in HIV infected children as in adults and can be an early predictor of progressive disease.[32]

c. ***Consequences of aberrant T cell activation:*** Some of the major reasons why immune activation is detrimental are summarized in Table 1.1.1. Collectively, the aberrant immune activation is detrimental to the host as the increased lymphocyte apoptosis results in decrease in CD4 T cells and T cell exhaustion resulting in impaired T cell function, dysregulated cytokine production marked by a deficiency in interleukin-2 (IL-2) production, functional abnormalities of cells of the monocyte/macrophage lineage, abnormalities in B cell function, and defects in natural killer (NK) function. Immune activation also exacerbates HIV replication, leads to skewed memory T cell generation and reduced regenerative capacity of immune cells.

Table 1.1.1: Why is aberrant immune activation "bad"?
Immune activation is the major driving force for HIV disease progression
• Increase T cell apoptosis and loss of CD4 T cells • Drives HIV replication by expanding cellular targets of activated CD4+ T cells • Depletes naive T cells and impairs thymus function • Promotes replicative senescence of T cells with failure of their renewal • Leads to immune exhaustion and blunts antigen specific responses • Results in fibrosis and disruption of lymphoid tissue architecture.

Chronic Immune Activation is one of the major causes of T Cell death: Uninfected T cells may die from apoptosis as a result of infection elsewhere. HIV-1 infection results in a state of chronic activation driven in part by the antigenic stimulus of HIV-1 and in part by antigen-independent mechanisms or cytokines released by APCs and activated T cells.[33] This process has been termed 'activation-induced cell death' or apotosis. Lymphocyte apoptosis in HIV disease is believed to result from direct and indirect effects of HIV and from the ensuing heightened state of lymphocyte activation. Both CD4 and CD8 T cells exhibit increased apoptosis.Increased apoptosis in lymphocytes of HIV infected children is well documented.[34] Accelerated destruction of CD4+ T cells is accompanied by reduced proliferation of progenitor cells, thereby disrupting the homeostasis depending on balanced production and death of mature progeny.

Another feature of chronic immune activation is the upregulation of PD-1 on virus specific T cells reducing their functionality.[30] PD-1 expression on CD8+ T cells correlates positively with plasma viral load and apoptotic activity and inversely with CD4 counts, cytokine production and proliferation. PD-1 expression on HIV-1 specific CD4+ T cells was also associated with disease progression.[31] The inhibitory receptor CTLA-4 is likewise associated with HIV-1 disease progression, and correlates negatively with IL-2 production and positively with viral load and may account for anergic CD4+ T cell responses in HIV-1 infection.[35]

B cells and Humoral Immunity

The second component of the adaptive immune system is constituted by B cells. Dependent on the presence of an appropriate microenvironment, progenitors of B cells also undergo a series of differentiation steps. The major function of B cells is to produce antibodies and provide a defense system against high-grade bacterial pathogens by secreting antibodies. For many antigens, such as protein antigens, the B cell response is dependent on adequate help from T cells. B cells are triggered by antigen to differentiate into antibody secreting cells and long lived plasma cells either in a T dependent or T independent manner. Antibody produced by B cells facilitates pathogen uptake by phagocytic cells and also has important properties to inactivate viruses and neutralize toxins.

In the context of HIV infection, two aspects of B cells are critically important. First, is the effect of HIV on generalized B cell function for protection against pathogens and eliciting vaccine induced antibody responses to a variety of childhood vaccines. Second, specific to HIV, the ability of the host to mount a serologic response against HIV that is protective.

It is well-established that HIV disrupts overall B cell functional responses with loss of memory cells, increased transitional B cells and blunted vaccine induced antibody responses.[36] The mechanism for this defect is still being investigated but it is well known that HIV interacts with B cells, which was first reported several years ago and evidence that HIV-1 infection causes immune dysfunction in B lymphocytes was established in adults and children. Pahwa et al demonstrated dysfunctional B cells in children[37] and showed that freshly isolated B cells from HIV infected patients were characterized by spontaneous immuno-globulin secretion as well as by unresponsiveness to activation signals. These two features are suggestive of an *in vivo* polyclonal B cell activation manifested as hypergammaglobulinemia *in vivo* with increase in the frequency of B-cell malignancies and *ex-vivo* evidence of increased cell turnover, expression of activation markers, and an increase in the differentiation of B cells to plasmablasts as measured by phenotypic, functional and morphological measures. The binding of HIV to B cells *in vivo* through interactions between the complement receptor CD21 (also known as CR2), and complement proteins bound to HIV and possibly also facilitate B cell mediated cell-to-cell transmission of HIV. In recent years, binding of microbial products to TLR receptors have surfaced as a mechanism for B cell activation, and production of antibody (endocab) against microbial products may diminish effects of microbial translocation.[31]

From the pediatric perspective, the B cell capacity to respond to bacterial infections and to vaccine immunogens for protection from childhood diseases are important B cell functions. In the pre-HAART era, intravenous IgG infusions on a monthly basis were beneficial for prophylaxis against bacterial infections (partially discussed in ref 11). Equally important is the ability to sustain memory responses to infections and following immunizations. Memory B cells are mostly regarded as longlived, resting, antigen-experienced cells that are rapidly inducible after exposure to cognate antigen. Studies evaluating responses to vaccine antigens in HIV infected children revealed defects in vaccine responses in children prior to CD4 depletion, demonstrating impairment of immunologic function in the presence of

normal numbers of T cells. Even children who had protective antibodies did not achieve or maintain antibody levels comparable with those of healthy children. The reason for poor antibody responses to routine childhood immunizations in HIV infection has become clearer with the emerging data that destruction of B cells by HIV occurs early in the course of infection.[38] An important observation in vertically HIV infected children was that initiation of HAART within the first year of life permits the normal development and maintenance of the memory B cell compartment.[39] In chronically infected children, however, although B cell defects can be reversed by HAART, one important exception is the loss of memory B cells, and several studies have shown that the increase in the number of CD27+ resting B cells following treatment occurs slowly and remains incomplete. Thus, it is recommended that children be revaccinated after HAART induced reconstitution to generate new immune responses and develop immunologic memory. Good revaccination results with tetanus, measles, mumps, and rubella have been observed in most children on HAART. Clinical trials to evaluate booster vaccines to encapsulated bacteria are ongoing.

While almost all HIV infected individuals develop an antibody response to HIV envelope and core proteins, the ability to demonstrate existence of neutralizing antibodies in laboratory assays has been limited. In newly infected persons, neutralizing HIV specific antibodies develop slowly, arising approximately 3 months after HIV transmission. To date few neutralizing antibodies directed to limited epitopes have been identified in naturally infected individuals, and the more potent ones also had self reactive components, limiting their utility for therapeutic purposes. Escape mutations in envelope are recognized as a cause of evading antibodies; by the time a host develops an antibody response the virus envelope has mutated so that circulating antibodies while capable of neutralizing earlier virus envelope is unable to neutralize contemporaneous isolates. The lack of neutralizing antibodies in infants has been linked to rapid disease progression.

New technologies are rapidly advancing the B cell field and recently novel epitopes eliciting neutralizing antibodies have been identified. Two new antibodies in particular are extremely potent and are generating a great deal of enthusiasm as major leads for immunogen design and for their potential utility as prophylactic antibodies in selected settings, such as in protection from breast milk transmission to infants. Clinical trials will be developed to test the feasibility and efficacy of various approaches. Non-neutralizing anti-env antibody responses of IgA and IgG isotype may also mediate antiviral activity via mechanisms such as ADCC or complement fixation. To be effective, HIV antibodies have to be present at the time of virus exposure to prevent the establishment of infection which is what vaccines aimed at eliciting protective antibodies are attempting. After HIV infection is established, the efficacy of anti-HIV neutralizing antibodies is not established.

The Innate Immune System During Pediatric HIV-1 Infection

The interface between innate and adaptive immunity is important in influencing the emerging nature of the adaptive immune response in response to pathogens. In acute HIV infection in adults, activation of the innate immune system is evident by the elevation of acute-phase proteins, cytokines and chemokines in plasma; a cytokine storm, consisting of IL-15, IFN-a followed by TNF, IL-18, IL-10 and CXCL10 and its ligand has been described.[9] It is not known if acute infection period in infancy is also associated with a cytokine storm.

Among cells of the innate immune system, NK cells and dendritic cells have been most studied. NK cells are believed to be important in HIV-1 infection because of their ability to kill virally infected cells. In addition, they produce large amounts of MIP-1a, MIP-1b and RANTES, ligands for CCR5. Through competitive inhibition of receptor binding, these chemokines block viral entry to target cells by R5-tropic viruses *in vitro* as well as *in vivo*. This is supported by an inverse correlation between chemokine-mediated blocking of HIV-1 replication and HIV-1 viremia.[40]

Further evidence in line with a protective effect of NK cells is the finding that genes involved in NK cell regulation play a role in control of viral replication and disease progression. Expression of certain HLA-B alleles and specific killer cell immunoglobulin-like receptor (KIR) haplotypes may either slow down, or promote disease progression.[41] HIV-1 actively down regulates HLA-A and HLA-B class I molecules on the surface of infected cells rendering them susceptible to NK cell-mediated killing. However, selective retention of HLA-C and HLA-E expression may prevent cell lysis and promote skewing of the NK cell repertoire towards cells with HLA-C specific inhibitory KIRs. Both acute and chronic untreated HIV-1 infection is associated with alterations in NK cell subset distribution, receptor expression and function.[41] In particular, untreated HIV-1 infection is associated with fewer CD56dim cytotoxic NK cells, and accumulation of a dysfunctional CD56–CD16+ NK cell population.[42,43] This subset displays substantially impaired cytolytic capacity and IFNg production, but maintains the capacity to produce MIP-1b. The expansion of this unconventional NK cell population is reversed with ART-mediated suppression of viremia and so are also many of the phenotypic alterations.[42]

The role of plasmacytoid dendritic cells (pDC) in anti-HIV immunity is mostly represented by the production of type I IFN in response to HIV infection *in vitro* and *in vivo*. Low circulating DC counts during chronic HIV-1 infection were found in the pDC population. This loss was correlated with plasma viral load or with peripheral CD4+T cell counts. pDC numbers correlated with lymphoproliferative responses against HIV-1 p24 in one study. In HIV infected children, pDC counts have been found to be lower in viremic children with a history of decreasing CD4+T cell percentages, compared with children with stable CD4 + cell counts and low expression of CCR7 in activated pDC was associated with disease progression.[44] A recovery in pDC counts, at least a partial one, seems to be obtained through HAART during chronic infection[45] as well as during primary infection, and sometimes correlated with a recovery in CD4 T cell counts and a decrease in viral load, but not in all studies. The correlation between high type I IFN production and low viral loads or high CD4 T cell counts indicates a role for these IFN in the control of HIV replication. IFN-a and – b have a strong antiviral activity *and induce* lysis of infected cells by APC, including DC. Type I IFN can also have indirect antiviral activities through its actions on the immune system and IFN- a enhances the survival of pDC in an autocrine positive loop. Type I IFN enhances MHC class I expression, which is down modulated by the HIV Nef protein on all cell types, including DC. This may help to keep recognition by CD8+ T lymphocytes in secondary lymphoid organs. IFN-a induced by acute viral infection *in vivo* stimulates antigen cross-presentation, through a mechanism involving direct stimulation of DC. Cross-presentation to CD8+ T lymphocytes is probably crucial in HIV-1 replication control.

All of these protective effects may have detrimental consequences, particularly the induction of apoptosis in uninfected CD4+ T cells. Cytotoxicity is mediated in part by tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL), which is induced *in vitro* on monocytes and DC by HIV, and which is elevated in the plasma of HIV-1 infected patients in parallel with viral load.[46] Incubation with HIV itself, live or inactivated, induces cytotoxicity in monocytes as well as in DC towards HIV-1 infected and uninfected CD4+ T lymphocytes. Type 1 IFN induced with by HIV in the thymus may upregulate MHC class I molecule expression on most thymocytes and be detrimental for their maturation.

Management

Diagnosis of HIV Infection in Infants and Children—When to Suspect HIV Infection

The key to diagnosis of HIV infection in a baby is knowing the serologic status of the mother. Thus, obstetricians and pediatricians should make every effort to determine the HIV status of pregnant women with the goal to: (a) prevent MTCT and (b) offer the best options to the offspring. The vast majority of infants born with HIV infection appear healthy at birth. Time of onset of symptoms varies, and many can go undiagnosed for prolonged periods if mother is not known to be HIV infected. Some children have minimal to absent symptoms early in life except for mild axillary lymphadenopathy which may not be picked up clinically. About 10 to 20 percent HIV infected infants will progress rapidly in the first year of life with symptoms such as failure to thrive, candidiasis, diarrhea, recurrent bacterial infections or opportunistic infection such as Pneumocystis jirovecci pneumonia (PCP). The majority of HIV infected children have a variable course and without treatment they will develop disease symptoms and die in the first few years of life with progressive CD4+ T cell lymphopenia, and a generalized state of immune activation with concurrent immune deficiency affecting innate and adaptive immunity. The progressive immune deficiency ultimately leads to the development of opportunistic infections, wasting, and death.

In instances where the mother is known to be HIV+, diagnostic testing of the infant is of vital importance, to rule in or rule out HIV infection.[2] Definitive diagnosis of HIV infection is made by virologic testing, using DNA PCR or HIV RNA in peripheral blood or dried blood spots, both assays with equal sensitivity. The sensitivity of these tests is about 20 percent in the first 2 weeks and >90 percent by 28 days. Thus diagnostic testing should be performed at 1 to 2 months (WHO recommendations are to test at 6 weeks. In the US testing is usually at birth, 14 to 21 days and again, at 1 to 2 months). If these tests are negative, a repeat testing at 4-6 months will rule out infection in non-breastfed infants. Establishing a "not infected" status is as important as establishing the status of infected. In places without facilities for virologic testing HIV antibody testing is commonly used. In uninfected infants, it takes 6 to 18 months before the test becomes negative. In infected infants, antibody positivity beyond 18 months establishes a diagnosis of infected. This delay in diagnosis robs a child of early ARV, if access to drugs is not an issue. An alternative approach could be to establish strong suggestive evidence by altered CD4/CD8 ratio[2,47] coupled with clinical evidence and use this to seek virologic diagnosis in selected cases, but will delay the diagnosis by 3 to 6 months. In breastfed infants repeat testing is required at intervals until a few months after cessation of breast-feeding. Guidelines for safe breast feeding should be followed.[48] Early treatment is clearly the best approach for the well-being of HIV infected infants, regardless of CD4 count or virus load or symptomology.

Differential diagnosis of rapidly progressive HIV in infancy includes primary immune deficiency diseases such

as severe combined immune deficiency (SCID). Clinical presentations of rapidly progressive HIV disease and SCID can be similar, with failure to thrive, oral candidiasis, diarrhea and PCP. As treatments are drastically different it is important to differentiate between the two. Axillary lymphadenopathy, hepatomegaly, and clubbing of fingers are common in HIV/AIDS. Hypergammaglobulinemia, CD4 T cell lymphopenia with reversal of CD4/CD8 ratio and normal to increased B cells are characteristic of HIV/AIDS. In infants with SCID, panlymphopenia with low T cells (often with high B cells in certain types of SCID) and hypogammaglobulinemia are the norm. Virologic testing will establish the diagnosis of HIV/AIDS.

ARV in HIV Exposed Uninfected Infants

A 6 weeks neonatal component of the zidovudine chemoprophylaxis regimen is recommended for all HIV exposed neonates to reduce perinatal HIV transmission.[48, 49] ZDV may be combined with additional drugs under guidance of a pediatric HIV specialist and discussion of the potential risks and benefits of this approach with the mother, preferably before delivery. To prevent PCP, all infants born to women with HIV infection should begin PCP prophylaxis at age 4 to 6 weeks, after completion of the zidovudine prophylaxis regimen. This is not necessary if HIV infection is presumptively ruled out. In HIV exposed uninfected children, occasional immunologic deficits without significant clinical consequences have been described, but the relevance of this is being investigated as a research topic. As such no immune monitoring is recommended.

ARV in HIV Exposed Infected Infants

In most infants infected *in utero* or at birth, HIV infection can be definitively diagnosed through the use of virologic assays by the age of 1 month and in virtually by age 4 months. Initiation of antiretroviral therapy is highly recommended for infants aged <12 months who are definitively diagnosed as being infected, regardless of clinical status, CD4 percentage, or viral load.[48] The benefits of starting within the first 6 months of life in survival of HIV infected infants were dramatically illustrated in the Cher study.[50] The goal of ART is to reduce plasma HIV RNA levels to below the limits of quantitation and to normalize immune status. In the absence of HAART, perinatally HIV infected infants progress more rapidly than adults, and about 10 to 15 percent died within the first year of life. The median time to AIDS for the remaining 75 percent was 7 years in the European collaborative study of natural history of vertically acquired HIV-1 infection, published in 1994. All HIV infected children should have immunologic monitoring and if possible virologic monitoring at regular intervals.

Immunologic Classification and Immune Monitoring

Children have relative lymphocytosis and thus their norms for CD4 cells are different from adults.[47,51] This is an important consideration in developing treatment strategies and in assessing immune competence. For routine follow-up of HIV infected infants, monitoring of the CD4 lymphocyte count and HIV RNA are recommended. The age of the child must be considered when interpreting the risk of disease progression based on CD4 percentage or count and plasma HIV RNA level.

Based on their CD4 cell counts, children of different ages can be categorized into different immune categories defining the degree of immunosuppression (Table 1.1.2). The 1994 CDC definition used CD4 percent to group all HIV infected children under age 5 years into 3 immunologic categories: normal (CD4 >25 %), mild moderate suppression (CD4 15 to 24%) and severe suppression (CD4 <15%). The more recent WHO classification[56] and the guidelines for ARV treatment [48] have taken into account CD4 data compiled from 3942 children living with HIV from United States and Europe participating in 17 studies[57] which provides estimates of CD4 and age-related risk of progression to AIDS or death. The revised WHO classification has developed thresholds for immunodeficiency that reflect the increased risk of progression and death that younger children face at a similar CD4 counts compared to older children. Children are divided into three age groups each with distinct CD4 thresholds.[56] WHO guidelines of 2007 lists CD4 percent criteria for advanced disease in HIV infected children <5 years of age as <30 percent for age <12 months, <25 percent for <3 years, and <20 percent for children at ages 3 to 5 years. Immunologic staging forms the basis for immune monitoring.

Until the HIV status is established, all infants need to be monitored immunologically at regular intervals as discussed below. Once HIV infection is ruled out, routing follow-up of HIV uninfected infants does not require immunologic monitoring. For HIV infected children, clinical, immunologic and virologic monitoring should be performed concurrently. If virus load monitoring is not possible then CD4 lymphocytes and clinical evaluation can also yield important information. Clinical monitoring of HIV associated symptoms based on the revised WHO guidelines[56] consists of 4 stages:

1. Asymptomatic, 2. Mild symptoms, 3. Advanced symptoms, 4. Severe symptoms.

a. ***Immune Monitoring in HIV infected Children <5 years of age:*** Where resources are available, T cell lymphocyte subsets and plasma HIV RNA should be obtained at baseline (and 1 to 2 months after initiation of a new

ARV regimen as a measure of response to treatment). They should subsequently be repeated every 3 to 4 months to make sure immune function and virologic control is being maintained, or more frequently in children with clinical deterioration or rapid decline in CD4 count. More frequent CD4 cell and plasma HIV RNA monitoring may also be considered in infants less than age 6 to 12 months. Repeat testing is also recommended to confirm an abnormal value; or when initiating or changing therapy. In children under age 5 years, CD4 percentage is preferred for monitoring immune status because of age-related changes in absolute CD4 count in this age group. In the absence of virus load monitoring, or in the absence of ARV, CD4 counts alone or in association with CD8 T cells together with clinical evaluation can provide useful information related to disease progression.[57] Frequency of testing should be every 3 to 4 months to make decisions about need for starting ARV, or changing ARV based on CD4 thresholds in accordance with the WHO guidelines[56] or the US ARV guidelines.[48]

b. ***Immune Monitoring in HIV infected Children >5 years of age:*** Predictive value of absolute CD4 cell count for risk of death or AIDS/death in HIV infected children age 5 years or older is similar to that observed in young adults, with an increase in the risk of mortality when CD4 cell count fell below 350 cells/mm^3,[48] which is the CD4 cut-off below which patients are classified as having advanced HIV disease. Frequency of immune monitoring should be every 3-4 months for reasons cited earlier.

Immune Reconstitution in HIV Infected Children

With potent ARV therapies, dramatic clinical benefits, including prolongation of life, suppression of HIV, and improvement in CD4 T cell counts, are being seen in children and in adults. Important questions have arisen as to whether the increase in CD4 T cells translates into immunologic reconstitution.

The administration of HAART reduces HIV-1 load efficiently to undetectable levels and increases the number of circulating CD4+ T cells in children as well as adults.[52] Although HAART does not eradicate HIV-1, due to a persistent low level of viral replication and the longevity of latently infected cells, it allows for substantial recovery of immune function. Immune reconstitution after HAART initiation is different in children. While, in the adult, it is a biphasic process with an initial rapid increase in memory CD4+ T cells followed by a slower and smaller increase in naive CD4+ T cells in children immune repopulation involves mainly naive cells, due probably to more efficient thymopoiesis. Studies of T cell receptor excision circles (TRECs) and T cell receptor (TCR) repertoire have yielded encouraging results.[14] Lymphocyte proliferation assay (LPA) responses to recall antigen candida recover first, but tetanus responses are slower to recover.

Clinically, in studies of child comparing pre HAART to post-HAART era, reduction in the incidence of opportunistic infections (Pneumocystis jiroveci pneumonia (5.8 vs 0.3 cases per 100 patient-years), recurrent bacterial infections (4.7 vs 0.2 cases per 100 patient-years), extraocular cytomegalovirus infection (1.4 vs 0.1 cases per 100 patient-years), and disseminated nontuberculous mycobacterial infection (1.3 vs 0.2 cases per 100 patient-years) were noted in children born from 1986 to 1998 who were monitored until 2004 in the Perinatal AIDS Collaborative Transmission Study, sponsored by the Centers for Disease Control and Prevention.[53] In addition, prolongation of the time to the first opportunistic infection was noted in the post-HAART period.

Even with HAART, HIV specific immune responses do not always improve. Humoral immune responses to vaccine antigens wane in HIV infected children. With normalization of the T cell repertoire and the active production of new T cells, it is expected that reimmunization will lead to an effective immune response. The important point is that early institution of HAART preserves the immune system. HAART initiation when a child is immunocompromised may not fully restore immune competence. Caregivers have to be cognizant of danger of the immune reconstitution inflammatory syndrome (IRIS) due to rapid immune reconstitution when ARV is first initiated in a child with severe immunodeficiency.[54] Failure of immune reconstitution may be a result of associated persistent immune activation due to microbial translocation,[31] impaired thymus regeneration or impaired lymphocyte proliferative capacity. Restoration of memory T cells is considered one of the most important components of immune reconstitution.

Childhood Immunizations in HIV Infected Children

All childhood vaccines should be given to children with HIV infection if the immune system does not show evidence of immune suppression. Live viral and bacterial vaccines should be withheld if there is immunosuppression. Immune suppression is determined on the basis of CD4 counts and age. Vaccine guidelines are reviewed in reference[55] and in the Pediatric Infectious Disease Guidelines in the Red Book. If children are not on ARV, there is a strong likelihood that vaccination will activate T cells and lead to increase in plasma virus load. However, these increases are usually transient and the risk of infection with the pathogens is usually greater than that resulting from the transient viremia. HIV infected children can be given Hepatitis B, Diphtheria, Tetanus, Acellular pertussis; Inactivated polio (live oral polio vaccine should

not be used even in household contacts because it is shed); Measles, mumps, rubella vaccine (exception: severely immunocompromised children); *Haemophilus influenzae* type B, Hepatitis A should be considered, especially in children with hepatitis B and C and other liver dysfunction, and in travelers; Pneumococcal conjugate vaccine (preferred to polysaccharide); Seasonal influenza; Varicella (only children who are asymptomatic and have normal CD4 count for age, and uninfected, nonimmune household contacts). Vaccine trials in children have been conducted and some are ongoing in various centers for MMR Varicella, Pneumococcal; DTaP; HPV (girls and boys); Hep A; Hep B; Rotavirus; H1N1; Seasonal Influenza; Meningococcal vaccines. Certain vaccines, including MMR, Pneumococcal, Rotavirus have been evaluated in HIV infected children <2 years. Certain vaccines (e.g. Pneumococcus conjugate vaccine) can be administered to pregnant women and have the advantage of protecting the mother and the infant through transplacental passage of IgG.

Specialized Laboratory Evaluation of HIV Infected Children

CD4 T cells is the most important immunologic measure for follow-up of HIV infected children, as described above, and is sufficient for monitoring a child on ARV or for determining time to start or time to change ARV, together with virologic testing. if possible. Tests summarized below can offer further insight into state of immune competence but should be considered mandatory. Most of these have been discussed earlier in the chapter.

Quantitative Analysis

Besides CD4 T cells, other lymphocyte subsets that may be quantitated include CD8 T lymphocytes, natural killer (NK) cells, and B lymphocytes. The ratio of CD4 T:CD8 T lymphocytes provides an idea of the degree of lymphocyte imbalance; normally the ratio is, >1 but may be much higher in young infants. In the setting of HIV infection, this ratio is reversed.

Flow cytometry allows for analysis of maturation subsets of T and B cells. For CD4 and CD8 T cells these markers allow the identification of naïve, central memory, transitional, effector memory, and terminal effector cells. For B cells, naïve, transitional, activated and memory cells as well as plasma cells and plasmablasts can be quantitated. Markers of exhaustion (PD-1, CTLA-4), and of immune activation (HLA-DR and CD38) and cell proliferation (Ki67) can be incorporated in the flow panels. Of these, immune activation markers are simple to incorporate in a flow cytometry laboratory and could prove especially insightful about disease progression, as discussed earlier. Similarly studies of gut microbial translocation can also provide meaningful information in relation to immune activation. Analysis of various CD4 T cell subsets (TH-1, TH-2, TH-17, IL 21 producing) is based on intracytoplasmic cytokines and CD107a is a degranulation marker as a surrogate for cytotoxicity. CD4+ Regulatory T cells have distinct markers CD25 bright FoxP3+ to characterize them. Similarly phenotypic analysis of natural killer cells and dendritic cells can be performed with small quantities of blood.[44]

Functional Analysis

Levels of one or more classes of immunoglobulins (IgG, IgM, IgA, IgE) are usually increased in HIV infected children and are indicative of excessive B cell stimulation. With control of HIV replication, these levels decrease to normal or near normal levels. In rare cases, hypogammaglobulinemia has been reported to occur in association with HIV infection.

Skin testing for delayed-type hypersensitivity (DTH) can be performed with one or more antigens to which the child has been exposed. The most commonly used antigens are diphtheria and tetanus, which almost all children have been exposed to through vaccination, and *Candida*, a common infection during infancy. Generally, approximately 60 to 90 percent of healthy children respond well to diphtheria and tetanus antigens but have age-dependent responses to *Candida* antigen. Testing involves intradermal injection of the antigen with the site assessed for induration after 48 hours.

In vitro mitogen and antigen stimulation are used as relatively crude measures of cellular immunity. These tests may be useful if assessment of cellular function is needed. This testing is not available in all laboratories. In *in vitro* mitogen and antigen stimulation for lymphoproliferation, the patient's peripheral blood mononuclear cells are cultured with mitogens, such as phytohemagglutinin, concavalin A, pokeweed mitogen, and other antigens to which the patient has been exposed, including tetanus toxoid and *Candida albicans*. A stimulation index is then calculated. Impaired lymphoproliferative responses to antigens are common and precede the loss of responsiveness to mitogens and CD4 depletion in HIV infected children. Such abnormal function correlates with the development of opportunistic and bacterial infections.

By far the most commonly used functional analysis is of polyfunctional T cells (PFT) for CD8 and CD4 subsets based on their ability to secrete multiple cytokines and additional markers by flow cytometry. Ideally 8-10 color analysis is required using sophisticated instrumentation. Other functional analyses of antigen specific T cells in relation to host HLA alleles and virology investigations for HIV mutations can provide additional insight into risk of disease progression, but should be considered as specialized research tools.

Functional analysis of B cells include the determination of humoral responses following vaccinations. Production of antibody responses to vaccine antigens, such as tetanus, diphtheria, *Haemophilus influenzae* type b, hepatitis B, measles, mumps, rubella, and pneumococcal antigens, can be tested 1 month following vaccine administration for the determination of a primary response. Follow-up testing can be considered every 5 years to determine the presence of long-term humoral immunity and to guide decisions regarding revaccination.

Exvivo testing for IgG or antibody secretion is evaluable using the Elispot assay. B cell phenotype and function tests are not readily available but can provide valuable information on memory cell functional capabilities and are useful tools in specialty laboratories.

Flow cytometry assays for functional assessment of natural killer cells and dendritic cells can be performed incorporating phenotype and stimulus induced cytokines or degranulation for NK cells.

Case Studies

CASE 1

A 2-year-old child presents for routine well baby clinic visit. The child is in 15th percentile for height and 5th percentile for weight. Examination is unremarkable except for palpable axillary lymph nodes, and mild hepatosplenomegaly. Mother is in good health but states that her husband is having frequent diarrhea and losing weight. She has another child 6 yrs of age who is well. The physician orders complete blood count with sedimentation rate, chemistries and stool examination. Only positive finding is elevated sedimentation rate, mild anemia and elevated globulins with altered albumin to globulin ratio. The combination of elevated sedimentation rate and high globulins due to hypergammaglobulinemia should raise suspicion of a chronic infection such as HIV/AIDS. Subsequent testing revealed high IgG, A and M. The child tested positive for HIV serology as did the mother and father. The index case here is the father who transmitted HIV to his wife who in turn transmitted it to the child. All were unaware of their diagnoses until the child was identified as HIV+.

Recommended course of action: Perform assessment in child for CD4 counts and virus load if feasible. Follow treatment guidelines of WHO based on clinical classification and CD4 count to determine when to start antiretroviral treatment. Monitoring every 6 months or 4 months with CD4 counts and VL is recommended. Refer parents to ID specialist.

CASE 2

A 6 month infant is admitted with respiratory distress. Examination reveals a child with obvious failure to thrive, oral thrush and diaper rash. Chest X-ray reveals pneumonia and blood gases show hypoxemia. There is no known history of illness in the parents and the infant has no siblings. Differential diagnosis here is that of a primary cellular immune deficiency versus HIV. HIV tests in the baby show positive results for serology, which indicates that the mother is infected. Subsequent immunologic analysis reveal decreased CD4 count (15%) and high virus load, 700,000 copies/mL.

Recommended course of action: Treat presumptive PCP while diagnosis is being established. Once infant is stable, start ART if access to therapy is possible. Refer mother and father to ID specialists.

CASE 3

A 4-year-old child is diagnosed with TB. He has severe pulmonary TB with effusion and CD4 count is 8 percent with absolute CD4 of 120 cells. Concurrent HIV is suspected and the antibody test comes back positive. The physician in charge starts therapy for TB and HIV together. Initially the TB symptoms attend to improve. Four weeks after treatment initiation the TB appears to take a turn for the worse. CD4 count is now 15 percent with absolute count of 300 cells. The family is alarmed that the TB is worsening. What is the best course of action: Stop TB meds, Stop HIV meds or Start steroids?

This case is presumptive IRIS (immune reconstitution inflammatory syndrome) due to inflammatory reaction against TB Bacillus as a result of rapid immune reconstitution. Differential diagnosis: Worsening of known TB due to inadequate or inappropriate therapy; new infections (e.g. bacterial sepsis); Medication reaction.

The right approach at this time would be to initiate steroids and continue both TB and ARV treatments. Ideally the TB treatment should have been started first, followed about 6 to 8 weeks later by ARV. BCG IRIS is another complication frequently seen in previously asymptomatic infants or children who are started on ARV therapy when they are severely immunocompromised and who show rapid increase in CD4 counts.

Summary

Some of the major immune defects in HIV infected children are summarized in Table 1.1.3.

The main points regarding the immune system are as follows:

- The immune system fails in HIV infected persons including children because of the following main reasons:
- Virus mutation and immune escape—because immune response is too weak, too narrow or misdirected (like monotherapy)
- Envelope protein structure avoids antibody-mediated neutralization
- Immunologically "silent," latently infected cells persist despite HAART

Table 1.1.2: WHO immunological classification for established HIV infection

HIV associated immunodeficiency	Age-related CD4 values			
	<11 months (% CD4+)	12-35 months (% CD4+)	36-59 months (% CD4+)	>5 years (absolute number per mm^3 or % CD4+)
None or not significant	>35	>30	>25	>500
Mild	30-35	25-30	20-25	350-499
Advanced	25-29	20-24	15-19	200-349
Severe	<25	<20	<15	<200 or <15

Table 1.1.3: Summary of immune defects in chronic HIV infection in children

Innate immunity
• DC: Defects in plasmacytoid DC function and CCR7 expression • NK cells: Impaired killing
T cells
• Phenotype: Imbalance of maturation subsets, decreased naive cells • Polyfunctional T cells: Reduced, specially IL-2 secreting cells • T cell proliferation: Reduced in response to antigen stimulation • CTL effector molecules perforin: Decreased in CD8 T cells • Immune Activation: Increased markers of activation, exhaustion and apoptosis • TRECS: Reduced
B cells
• Polyclonal hypergammaglobulinemia • Loss of memory cells • Decreased antibody responses to childhood vaccinations, exhaustion

- HIV specific CD4+ T-helper cells are preferentially targeted by the virus
- Several strategies are used by the virus to impair immunity (e.g. Nef interferes with antigen presentation).

Key Messages

- Identification of HIV infected women prior to and during pregnancy should be attempted in all cases and interventions given to prevent MTCT.
- Early diagnosis of HIV infection status in HIV exposed infants is of paramount importance and in instances of confirmed infection, treatment should be initiated as soon as possible in infancy to preserve the immune system.
- Risk of infection transmission by breastfeeding should be discussed and appropriate advise given to breast feed or not based on socioeconomic status and ARV interventions in mother or baby.
- Basic immunologic monitoring with CD4 cell counts should be faithfully followed in all HIV infected children regardless of therapy. Additional testing for virus load, specialized virologic and immunologic assays may enhance the overall assessment of immune competence. If facilities are limited, markers of immune activation are simple and potentially of great value in follow-up.
- Routine vaccine strategies should be followed except for situations outlined above, and revaccination should be considered, especially in children who were not given ARV during infancy.
- Natural history studies to identify slow progressors and virologic controllers, and values of CD4 counts in relation to disease progression should be collected for the Indian pediatric population to develop appropriate cut-off thresholds.

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1.2

Virology and Laboratory Diagnosis of HIV Infection in Infants and Children

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Introduction and Importance

The diagnosis of HIV infection in an infected infant or child requires an integrated system of clinical, programmatic and laboratory services, continuously monitored for quality and outcome. Challenges range from the ethical, such as issues of consent; to the technical, such as the limitations of the tests and test strategies for infants; to the programmatic, such as funding and instituting appropriate therapy in a timely manner.[1]

Routine neonatal testing and improved prenatal HIV screening have been shown to be cost-effective and to result in the prevention of HIV transmission in a large percentage of cases. Testing identifies HIV infection in pregnant women, newborns, infants, and children and allows appropriate treatment and intervention strategies to be implemented that decrease newborn HIV infections, treat infected infants, and save healthcare costs. In particular, the availability of rapid HIV tests has proven valuable in the identification of HIV infected women in labor, but without a known HIV status, so that antiretroviral prophylaxis can be given immediately.[2-4] Although the laboratory diagnosis of HIV in the mother is relatively easy and should be routine, diagnosis of HIV in the exposed infant is more difficult, primarily because of the persistence of maternal antibody. In addition, if breastfeeding is practiced, the diagnosis can be complicated because of the potential for infection in the infant after birth. However, with appropriate testing strategies, along with clinical assessment, the status of infants born to infected mothers can be established with confidence.

There are several benefits to determining HIV infection status as early as possible in exposed infants.[5-7] Aggressive antiretroviral therapy and prophylactic cotrimoxazole can be initiated in a timely manner; clinical, immunologic, and virologic markers can be monitored properly; and adequate social support provided. In addition, there may be the opportunity for the child to be enrolled in clinical trials.

In this chapter, we consider how the biology of HIV infection in the infant influences testing methods and strategies, the utility of clinical methods for diagnosis, and integration of infant diagnosis into maternal-child HIV care. We also consider diagnosis in the older child, including aspects such as who should be tested and issues of consent and disclosure.

Rationale for Early Diagnosis: The Natural History of Untreated HIV Infection in Infants and Children

Rationale for Early Infant Diagnosis

The primary rationale for prompt diagnosis of HIV infection is the often rapid progression of HIV in the untreated infant and young child. Early treatment with highly active antiretroviral therapy (HAART) after the rapid and accurate diagnosis of HIV exposure or infection in infancy is an essential component for the care of HIV infected women and their infants. The benefits of early infant diagnosis are many, and importantly, include keeping the family engaged in care at a time when many women are lost to follow-up. Because the majority of exposed infants are not infected, early infant testing often delivers good news at a time when women and their families may be overwhelmed with their own recent diagnosis. An additional reason to determine or exclude the diagnosis of HIV in the infant is to guide program effectiveness. In some settings, a negative virologic test has been used as a signal for weaning of the uninfected exposed breastfeeding infant. HIV infected infants, at least those not receiving HAART, fare poorly if not breastfed and so should not be weaned early.[8] However, early weaning of uninfected, exposed infants in many resource-

poor settings has not been of net benefit in HIV free survival.[8-12] Moreover, with clear evidence now of the protective effect of maternal HAART [13-22] or daily infant nevirapine,[16] practices that encourage early weaning are not advised.[23] Thus, virologic testing should not be used to automatically wean exposed, uninfected infants.

Timing and Early Natural History of HIV Transmission from Mother to Child

In unselected populations of HIV infected women not receiving any therapeutic intervention, about 7 percent of infants are infected before the onset of labor (as determined by virologic tests during the first few days of life), and approximately 13 percent are infected in the week or two before or during parturition (as detected by virologic tests at 4 to 6 weeks of age in infants with a negative virologic test at birth). Thus, about 20 percent of infants are infected through pregnancy, labor and delivery if there is no intervention. During a 2-year period of breastfeeding, an additional 15 percent or so of infants will become infected, so that in total, about 35 percent of infants become infected without intervention.[24] These risks are greatly modified by factors known to affect the risk of transmission. Increased risk is independently associated with lower maternal CD4 count or higher maternal viral load. Also, acute HIV infection during pregnancy is associated with an increased risk of perinatal infection, probably because of the transient high viral load during acute infection. Prematurity and prolonged rupture of fetal membranes also increase the risk of transmission, as well as innate immunologic factors; at this point these are not modifiable.

By far, the most important factor modifying the risk of transmission is the use of antiretroviral drugs. HAART, if adhered to, is highly effective for preventing transmission during pregnancy and delivery. Indeed, it is the relationship between the time of initiation of therapy in pregnancy and the observed rate of transmission that gives the best estimate of when transmission occurs during pregnancy. Transmission rates decrease with earlier HAART until reaching near zero with initiation of HAART by the beginning of the second trimester. Transmission during pregnancy and delivery occurring despite prescription of HAART is virtually always attributable to delay in onset of treatment, lapses in adherence, or otherwise ineffective or delayed virologic control.[25] Although the control of maternal viral load is probably important to reduce the risk of transmission, the observation that non-HAART antiretroviral regimens prevent transmission out of proportion to the decrease in maternal viral load,[25] along with animal experiments in pre-exposure prophylaxis, indicate that a major effect of maternal antiretrovirals is to administer the fetus with drugs that prevent the establishment of infection, in the event virus enters the fetus. Cesarian delivery performed prior to labor decreases the risk of transmission; however, because HAART is so effective, cesarian delivery is advised in the United States only if the maternal viral load near term is >1,000 copies/ml.[26]

During the first six months of lactation, mixed feeding with other liquids or solids increases the risk of transmission.[10] However, breastfeeding infants older than 6 months of age requires complementary foods. The observation that transmission rates are lower after 6 months than during early infancy in some [27,28] but not all[29] studies suggests that in older infants HIV transmission is not as affected by foodstuffs other than breast milk. Postnatal transmission during lactation is independently related to maternal CD4 count and plasma viral load.[30,31] Milk viral load appears to be the determining maternal factor.[32] The viral load in milk is much less than in plasma. However, mastitis facilitates viral entry or replication in milk, and mastitis may be evident clinically, or subclinically, as determined by increased milk sodium concentration.[33] Maternal HAART renders the milk viral load nondetectable in most women[34] and is effective for preventing transmission.[13-15] Transmission during lactation can also be prevented by giving the infant pre-exposure prophylaxis with a daily dose of nevirapine.[16]

Once infected, the fetus or infant does not control viremia well. Whereas most adults develop an effective immune response and rapidly control viremia, reaching a set-point of about 10,000 copies/ml within a few months, the viral load in the infected infant peaks within weeks to a median of around 300,000 to 1,000,000 copies/ml and then moderates only slightly to 100,000 to 300,000 copies/ml in the first year of life.[35] Figure 1.2.1 contrasts the peak and viral set point of newly infected adults and infants in Côte d'Ivoire.[35] This sustained, high viral load often has only a modest effect on the infant's CD4 count but has a

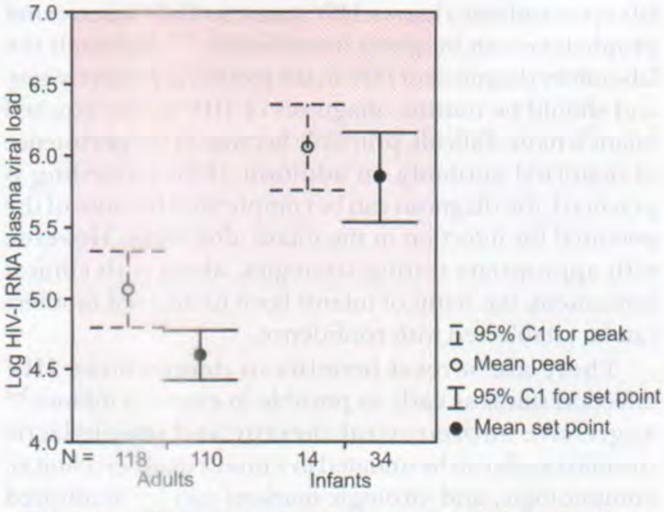


Fig. 1.2.1: Peak and viral set points for adults and infants

profound effect on the infant. In Africa, mortality in HIV infected infants climbs rapidly above that of the HIV exposed but uninfected infants where it rises after about a month of age.[36] Compounded by other perils of infancy in this setting and the effect of ill-health of other infected family members on care of the infant, the untreated HIV infected infant in resource-limited countries such as those in Africa has about a 35 percent risk of death by 12 months of life and about a 50 percent risk by 24 months.[36] Even with the availability of advanced medical care in the pre-HAART era in Europe, by 12 months, 26 percent had AIDS and 17 percent had died of HIV related disease.[37] Although there is a relationship between the CD4 count and the risk of disease progression or death, infected infants with a normal or near-normal CD4 count remain at high risk of disease progression or death.[7] In addition to the obvious manifestations of HIV disease, there is the more pernicious effect of subtle brain injury that is evident by significant differences in developmental testing between infected and exposed-uninfected infants by 6 months of age.[6] This difference is abolished by institution of antiretroviral therapy in early infancy.[6]

The natural history of HIV infection in the infant acquiring infection through breastfeeding is not quite as severe as with antenatal or intrapartum infection, but increasing mortality in breast milk-acquired infection is seen by about 7 months of age and thereafter roughly parallels infants with congenital infection of the same age.[38]

The high risk of early severe and subtle effects of untreated HIV infection and the efficacy of HAART in infants dictate the need for systems to ensure the diagnosis of HIV infection and the institution of HAART by 2 months of age. Monitoring for transmission during breastfeeding is also required as part of a comprehensive care package for HIV exposed infants in order to institute in a timely manner, as dictated by the natural history of late-acquired infection.

Methods for Diagnosis of HIV-1 Infection in Infants and Children

Background

The diagnosis of HIV infection in the older child or adult can be made in most cases with sensitive and specific serologic methods. However, serologic diagnosis in the infant is complicated by the omnipresence of maternal antibodies, which include those to HIV if the mother is infected. Placental transfer of maternal IgG begins at about 20 weeks of gestation and by term the infant has IgG levels that approximate maternal levels. IgM and IgA antibodies are not transported across the placenta. The detection of antibodies to HIV in early infancy, therefore, is valuable for identifying a child as having been born to an HIV infected mother, but does not signify infection in the newborn. HIV serology should be performed on any infant of a mother having an unknown status in order to identify the infant as HIV exposed and therefore potentially infected. As the infant ages after one year, the persistence of antibodies to HIV becomes increasingly likely to be due to infant infection. The definitive diagnosis of HIV in the exposed infant requires the detection of virus or viral products. Virologic tests using plasma may detect viral products such as viral antigen (e.g. p24), reverse transcriptase, and viral RNA as measured by methods such as reversed-transcribed PCR (RT-PCR) or nucleic acid sequence-based amplification (NASBA). When performed quantitatively, methods that detect these viral products in plasma measure the viral load. In addition, viral DNA can be detected in cells from an infected individual by PCR, and is currently the method of choice for infant diagnosis.

The diagnosis of HIV infection in newborns and infants may require a combination of clinical, serologic, and virologic methods.[1] Each is discussed below.

Clinical Diagnosis of HIV in Infants

In settings where virologic testing is not available or there is a delay in obtaining results, there is sometimes a tendency to accept the notion that HIV cannot be diagnosed and treatment initiated in infants until a positive serologic result has been obtained at 18 months of age (when maternal antibody decreases). It should be noted that diagnoses are made and treatment given for many other life-threatening conditions without the benefit of a definitive laboratory diagnosis. Some of the manifestations of HIV are seen in other common afflictions of infancy, while others are more peculiar to HIV infection.

In 2006, WHO recommended that a presumptive diagnosis of HIV can be made in a seropositive infant with a Stage 4 condition or with 2 of 3 of the following findings: severe pneumonia, severe sepsis, or thrush. Also, a CD4 count <20 percent of lymphocytes or a history of severe or fatal maternal disease (which suggests a high risk of transmission) provides supportive evidence for infection. A study of the performance of these criteria among hospitalized seropositive children <18 months of age in Kigali[39] found a sensitivity of 89 percent but a specificity of only 43 percent, yielding a positive predictive value of 63 percent and a negative predictive value of 77 percent. A study among hospitalized seropositive children <18 months of age from several sites in Africa[40] investigated whether the WHO criteria for severe disease could identify infected children for whom treatment was indicated according to 2008 WHO recommendations (treatment for all infected infants <12 months of age and children 12 to 18 months of age with <25 percent CD4, and children with

most stage 3 and all stage 4 conditions).[41] The prevalence of HIV in the study group was 47 percent. The 2008 WHO criteria for presumptive diagnosis correctly identified infected infants requiring ART with 69 percent sensitivity and 81 percent specificity; the positive predictive value was 71 percent and the negative predictive value was 79 percent. Thus, although there was a high prevalence of HIV among these ill seropositive infants, 31 percent of cases defined as needing therapy would be missed and 29 percent of cases presumptively started on therapy by this strategy would be uninfected children. Similarly, among symptomatic seropositive children <18 months of age in Nairobi clinics and hospital wards,[42] the 2006 WHO clinical and CD4 criteria for presumptive diagnosis of severe disease had a sensitivity of 84 percent but a specificity of only 41 percent in this population with a 60 percent prevalence, yielding a positive predictive value of only 32 percent, which is less than it would be, if simply all the children were presumed infected. It should be emphasized that these studies were among symptomatic infants, most seriously ill—it may be expected that these criteria would perform more poorly if applied to all exposed infants.

Accurately identifying HIV infected infants from among all exposed infants and not just those ill and in the hospital is an even greater challenge. A study in Zimbabwe monitored 3,297 infants of women diagnosed with HIV during pregnancy.[43] The clinical utility of diagnostic signs, as described in the WHO Integrated Management of Childhood Illness (IMCI), South African and Zimbabwean guidelines, and a proposed set of symptoms based on analysis of their data were evaluated at 6 weeks, 6 months, and 12 months of age. It was found that the sensitivity increased with increasing age, reaching 57 percent, 72 percent, and 61 percent for the presence of 2 or more signs from the IMCI, South African, and Zimbabwean guidelines, respectively, at 12 months, but the positive predictive values were less than 50 percent in this population in which 21 percent of infants were infected. Their model (2 or more symptoms of pneumonia, diarrhea, ear discharge, weight <3rd percentile for age, no weight gain over any 3 month period, generalized adenopathy, oral thrush, TB in infant or any family member, and weight less than the median for age) reached 68 percent sensitivity and 54 percent positive predictive value by 12 months of age. However, about a third of children remained undiagnosed and, as all infected infants should be treated, translates to almost half of presumptively diagnosed children would start therapy unnecessarily. In addition, by 12 months, the age at which there was the best diagnostic accuracy, roughly a third of infected children in this setting would be expected to have died.

HIV infected infants have higher CD8+ T cell counts and lower CD4+ T cell counts and thus lower CD4+ T cell percentages or CD4:CD8 ratios than exposed, *uninfected infants. However, among infected South* African infants, more than 50 percent had CD4:CD8 ratios within the normal range.[44] Looking at CD4 trends in infected or exposed, uninfected infants in Côte d'Ivoire, CD4 <25 percent of lymphocytes at 3 months of age was 87 percent sensitive and 78 percent specific[45] for identifying infected infants. However, for example, if the prevalence of infection among a group of exposed infants is 10 percent, using CD4 <25 percent to identify infected infants would achieve a positive predictive value of only 31 percent, while missing 13 percent of infected infants.

In addition to diagnosing infants infected during pregnancy and delivery, breastfeeding infants experience a long period of exposure. A study of breastfeeding exposed infants who were uninfected according to an RNA assay performed at 6 weeks of age investigated whether clinical signs could identify infants infected within the past 3 months.[46] Diarrhea, pneumonia, and otitis media were all more common in newly infected infants, but only a small proportion had these signs, and the resultant sensitivity and positive predictive values were very low.

An experienced clinician might be able to discriminate infected and uninfected children with greater accuracy than using simple CD4 and clinical criteria, but well-trained and experienced clinicians are scarce. Furthermore, considering the expense of antiretrovirals given unnecessarily to uninfected children, the emotional cost of an erroneous presumptive diagnosis, the loss of confidence in a system that makes erroneous diagnoses, and the cost in morbidity and mortality of missed diagnoses, early identification of infected infants by sensitive and specific laboratory methods is both effective and efficient relative to the alternatives.

Serologic Diagnosis of HIV in Mothers and Infants

Serologic methods are useful for the management of pregnant women, including those in labor, for identification of HIV exposure when maternal testing is not available, and as an adjunct to the diagnosis of HIV infection in exposed infants. However, because of the presence of maternal antibody in the infant's blood, it is not possible to determine whether a young infant is infected based solely on the presence of anti-HIV IgG antibodies that most serologic tests detect. Therefore, early diagnosis of infants usually requires the detection of viremia (by virologic testing), if the mother or newborn is seropositive, exposure has occurred and additional testing is indicated. If the mother or newborn is seronegative, HIV infection can be ruled out (except in cases of seronegative pediatric HIV infection discussed below).

Depending on the serologic method employed, maternal antibody can be detected in the infant's blood for 6 to18 months or longer. Testing during this time might detect maternal HIV antibody in the uninfected infant, producing a false positive result. Once maternal antibody

decreases to below a threshold characteristic for each test, the uninfected infant becomes seronegative (seroreversion). Although it is often assumed that serologic methods have no value until the infant is 18 months of age, the reality is more complex. How long maternal antibodies are detectable in the exposed, uninfected infant depends on the method of antibody detection. When using less sensitive tests, seroreversion can be expected in the first year of life, while when using highly sensitive methods, low levels of antibodies can sometimes be detected after 18 months of age. The time of seroreversion in the infant also depends on the level of maternal antibody present at birth,[47] which decays dependent on its half-life of about 23 days.

The standard for serologic diagnosis of HIV in adults and children is to perform a sensitive screening ELISA (or rapid test) for antibodies to HIV-1 (and often to HIV-2 also, depending on the kit used). Samples that are positive on the initial tests are then tested by a more specific test for antibodies to multiple HIV-1 antigens, such as the Western blot.[48] The Western blot detects antibodies to multiple HIV antigens that have been separated by electrophoresis and transferred to a nitrocellulose strip. The Western blot is interpreted as positive if antibodies to two of the three major HIV antigens, gp160/120, gp41, or p24, are detected. The result is indeterminate if one or more antigen bands are present but criteria for positive are not met. The result is negative if no bands are positive.[48] Causes of indeterminate Western blot results include false positive (in a low prevalence population the most likely explanation), early seroconversion in a recently infected individual, waning antibody levels in an exposed, uninfected infant, and waning antibody levels in a chronic infection—a situation that may be caused by the extremes of advanced HIV disease or by long-term viral suppression on therapy, a situation common in children who were started treatment in early infancy.

Rapid tests for antibodies to HIV are simple, inexpensive, and can be performed on-site by trained nonlaboratory personnel, characteristics particularly useful in the antenatal clinic and maternity service. A single rapid test is a sensitive screening test but is not completely specific. Positive rapid test results should be confirmed with an ELISA and Western blot if resources permit. In resource-limited settings, an algorithm using two different rapid tests may be used. The algorithm must have been validated against Western blot with a large number of samples from a similar population tested with the same two rapid test kits. Rapid tests can be performed within about thirty minutes (including the processing of the sample) and on-site, in contrast to ELISA tests which require substantial laboratory infrastructure and are usually performed at a different site from blood collection. For tests that allow the use of oral fluids, a swab is used to rub around the gums of the mouth.[49] The swabs contain a hypertonic salt solution that preferentially collects a transudate from the capillaries at the tooth-gum margin. This transudate (crevicular fluid) is derived from plasma and contains essentially the same components as plasma. Therefore, it is rich in IgG antibodies, although the concentration may be less due to the dilutional effect of saliva from the salivary glands. Oral fluid tests have not been validated for infants who have few or no teeth and hence little or no crevicular fluid. Following collection of the oral fluid, it is usually mixed with a diluent and used in the rapid test device using the same procedure as for plasma, serum, or finger stick specimens. Finger stick specimens are collected from a finger (or heel of infants) by lancet, and mixed with the diluent or applied directly to the device. Procedures differ from this point depending on the particular device. Some devices are considered as *flow-through*, where a drop of the specimen is applied directly to a membrane in the device that contains an HIV antigen. Anti-HIV antibodies in the sample, if present, bind to this antigen and are subsequently detected after washing using an anti-immunoglobulin reagent containing a signal-generating material (colloidal gold or an enzyme/substrate system). These flow-through devices require 1 to 20 minutes to complete. They do require several separate steps that must be followed exactly. Alternatively, many rapid tests use a *lateral flow* principle, where the sample is applied on a membrane at one end of the device, mixes with an antigen conjugate that contains the signal-generating material, and the complex migrates along the membrane where it is captured downstream by another immobilized antibody (2nd generation assays) or another antigen (3rd generation assays). These lateral flow assays are usually "one step" procedures that are simpler to perform and usually require 19 to 20 minutes. Other types of rapid assays (e.g. dipsticks and agglutination assays) are available also. Rapid tests and their characteristics have been reviewed.[49]

Although rapid HIV tests are simple to perform, procedures must be adhered to strictly. A recent report has indicated a poor sensitivity of several rapid HIV tests under field conditions.[50] However, the tests performed well under laboratory conditions, indicating that it is essential that persons using these tests (e.g. nurses) be well trained and monitored for proficiency.

Rapid tests are particularly useful for testing the mother in order to provide results in a clinically relevant time frame for intervention to prevent transmission. Results from these rapid assays can usually be obtained within 20 minutes using serum, plasma, venous whole blood, finger stick blood, or oral fluids. Facilities providing delivery services should have 24-hour availability of rapid testing for women who do not have documented recent test results. Sensitivities for diagnosis of adults are similar to ELISAs.[49] As with all screening assays, nonreactive results by rapid tests do not necessitate supplemental testing, but reactive results should be confirmed using a

more specific assay such as the Western blot or an alternative testing algorithm (e.g. a combination of different rapid tests). Because supplemental testing (e.g. with Western blot) may require several days to 1 week prophylactic antiretrovirals should be given while awaiting results of a confirmatory test.

There are two critical characteristics of serologic tests used for the diagnosis or the exclusion of HIV infection in exposed infants. One is the sensitivity for ruling out HIV infection at a particular age, i.e. a highly sensitive test will not miss any infected individuals. The second is the specificity for the diagnosis of HIV; this is for ruling out false positive results, i.e. a high specificity will produce few false positives. Several studies have followed exposed, uninfected infants to determine at what age serologic tests yield negative results (Table 1.2.1). The timing of seroreversion varied between studies. In the studies of Palasanthiran[51] and Moodley,[52] all uninfected infants were seronegative by about 15 months of age. Other studies found almost all uninfected infants to be seronegative by about 18 months of age,[47,53,54] yet others found a significant minority to be seropositive past 18 months of age.[47,55,56] In the only direct comparison of multiple methods, all but one rapid test kit yielded negative results in most uninfected infants between 7 to 12 months of age. The Abbott Determine rapid test and an Abbott ELISA remained positive in about half of the samples from 12 month old infants.[57] Differences in timing of seroreversion may best be explained by differences in assay sensitivity. Thus, the 18 month age often quoted as the point at which exposed, uninfected infants should have seroreverted must be qualified. If a less-sensitive rapid test is being used, uninfected infants should have seroreverted by 15 months of age. If more sensitive tests are used, a few uninfected infants remain positive at 18 months of age. The critical point is to know the sensitivity of the assay being used and not to rely on a single screening test but to use a second test, such as a Western blot or a validated, less sensitive second rapid test.

The specificity of serologic tests must also be considered when attempting to identify HIV infection in newborns. Positive serologic results on uninfected children over 15 to 18 months of age may be false positives due to cross-reacting antibodies if the testing methods are not highly specific. Thus, positive results on a single rapid test in children 18 and 21 months of age, as reported in a study from Malawi [53] might not be due to maternal antibody or infection but rather to cross-reactive antibodies. In a study from Vietnam [56] it was noted that when a second, different rapid test was performed, only 0.4 percent were seropositive at 18 months and none at 24 months. The negative results with one rapid test on samples that were positive with a second test could be due to a lower sensitivity of the first test to very low levels of maternal antibody, or to greater specificity with fewer false-positive results.[49]

Titers of maternal antibodies to HIV decay in exposed, uninfected children.[47] Perinatally infected infants also show a decline in antibody titers, but these begin to rise around 5 months of age.[51] However, differences in antibody levels between infected and uninfected exposed infants are not apparent until several months of age, too late to make an early diagnosis, and the diagnostic accuracy is not adequate to be useful for routine diagnosis.[58]

Not all infected infants have consistently positive results on serologic assays. Seronegative HIV infection has been described in adults; studies documenting the prevalence of seronegative HIV infection in children are summarized in Table 1.2.2. However, in a study of 109 HIV exposed children who had seroreverted, none were found to be infected by virologic PCR tests.[59] In the authors' experience, seronegative HIV infection has been seen only in children with advanced or rapidly progressive disease, apparently too immunocompromised to produce HIV specific antibodies.

Because IgM and IgA are not transported across the placenta, they have been investigated as an indicator of the infant's serologic response to HIV infection. The presence of HIV specific IgM in the newborn's blood implies that there is new antibody production in response to infection of the infant. However, most assays for the detection of IgM antibodies have not been shown to produce consistent results, and therefore they are not generally used.[49] Further, even in many seroconverting adults, IgM antibodies cannot be reliably demonstrated. HIV specific IgA in the infant is associated with infection. In one large study, the sensitivity and specificity of the IgA assay for children older than 3 months were 97.6 percent and 99.7 percent, and the positive and negative predictive values were 99.4 percent and 98.7 percent, respectively.[64] However, initial enthusiasm for this approach was tempered as it became clear that the appearance of HIV specific IgA lagged behind the appearance of directly detectable virus and was not sensitive enough to diagnose infants in the first several weeks of life.

Unfortunately, there are no published thoroughly validated algorithms for serologic diagnosis of older infants in settings where there is a reliance on inexpensive rapid tests. The performance characteristics of assays described in the references reviewed here can be used as a guide, but further studies are needed to precisely define test performance characteristics in specific populations. The use of serologic assays in diagnostic strategies is explained below in Section: Diagnostic Strategies.

Table 1.2.1: Time to seroreversion in uninfected HIV-1 exposed infants

Method	*Population*	*N*	*Results*	*Reference*
ELISA	Puerto Rico	84	Seroreversion at mean 11.6 ± 3.4 SD months; range 4.1-19 months	(47)
Western blot		51	Seroreversion at mean 15.8 ± 2.9 SD months; range 10.4-21.8 months	
Particle agglutination (Serodia)	Australia	11	Seroreversion at median 13.3 months; range 10.4-15.6 months	(51)
Rapid test (Determine or Stat-Pak)	Uganda	133 77 88	73% seronegative by 6-9 months 88% seronegative by 9-12 months 87% seronegative by 12-18 months	(55)
ELISA (Genscreen then Murex if Genscreen positive)	Vietnam	273	Cummulative seronegative by Genscreen (Genscreen negative or Murex negative) 22% (70%) at 12 months 92.8% (99.6%) at 18 months 99.6% (100%) at 24 months 100% at 30 months	(56)
ELISA (Abbott)	Malawi	892 999 1001	95.3% seronegative at 15 months 98.1% seronegative at 18 months 98.2% seronegative at 21 months	(53)
Rapid tests (7 tests) and ELISA (Abbott)	South Africa	289	40% seronegative at 12 months with ELISA 50% seronegative at 12 months with Determine rapid test 90-100% seronegative at 12 months with UniGold, First Response, OraQuick, SmartCheck, Pareeshak, or Insti rapid tests	(57)
ELISA and Western blot	US	151	98% seronegative at 18 months	(54)
ELISA	South Africa	77	94.5% seronegative at 12 months 100% seronegative at 15 months	(52)

Table 1.2.2: HIV infection in seronegative infants and children

Number of infected children tested	*Results*	*Reference*
Case report	PCR positive at 4 months, seronegative by ELISA and WB at 4 and 10 months of age. Mother probably infected late in pregnancy	(60)
34	5/34 (14.7%) of infected infants in a prospective cohort of exposed infants had transiently negative Western blot results between 6-10 months of age. Symptoms and CD4 counts varied from near normal to severely affected.	(54)
85	9/85 (10.6%) infected children (clinic series) had a negative ELISA	(61)
104	1 transiently seronegative at 7 months of age	(62)
77	8/77 (10.4%) seronegative and 4/77 (5.2%) indeterminate in a prospective study of exposed infants; 5 of these 12 had rapidly progressive disease	(63)
64	2/64 (2.5%) seronegative with repeatedly positive culture; not symptomatic	(37)

Virologic Diagnosis of HIV in Infancy

The limitations of clinical, immunologic and serologic methods for the diagnosis of HIV in exposed infants have lead to a focus on virologic methods that directly detect virus or viral products for an early diagnosis. In most instances of vertical transmission of HIV there is a burst of viral replication in the weeks after infection that is even greater than that seen in adults,[35,65-67] suggesting that diagnosis can be accomplished by measurement of virus or viral products in plasma. The detection of three different viral products in plasma has been used for infant diagnosis: HIV-1 p24 antigen, reverse transcriptase activity, and viral RNA. When quantified, such assays measure the plasma *viral load*. Virally encoded DNA in cells from the subject can also be detected by PCR, and its use is the most common diagnostic method for assessment of infection in exposed infants. Assays for viral RNA or DNA are usually referred to as nucleic acid tests. The measurement of viral products in plasma, whether antigen, reverse transcriptase, or viral RNA, has the theoretical advantage of detecting greater amounts of viral products in the plasma as compared with an assessment of DNA

from cells. Although infants usually develop very high levels of circulating virus within weeks of infection, methods that measure free virus in plasma are affected by antiretroviral therapy, to the point that HAART, by design, may render the level of viral products in the plasma undetectable, even by ultrasensitive viral load methods. Antiretroviral therapy also lowers the frequency of cells latently infected with HIV DNA, but not as greatly or rapidly. A discussion of each of these viral markers is presented below. The methods have been described in detail elsewhere.[49]

Detection of viral RNA in plasma: In contrast to qualitative RNA assays that identify infection, quantitative HIV RNA detection methods (viral load assays) are used to monitor viral replication to determine response to therapy and disease progression. These assays are useful to identify and quantify HIV viremia in pregnant women to guide treatment strategies for reducing the viral load, which is associated with decreased risk of transmission to the newborn.

RNA measurement may detect infection in the newborn earlier than DNA PCR because extracellular HIV RNA increases dramatically in newborns soon after infection.[65-67] The predictive value of a specific HIV RNA level for disease progression and death for an individual child is poor, especially in the first year of life, and so the viral load should not be used to select infants for treatment—all infected infants should be treated. The performance of viral load methods for infant diagnosis was reviewed by Read.[48] Defining an age at which the sensitivity of RNA testing is at or approaches 100 percent is difficult because of differences in age categories in the published reports. However, by 6 weeks, the sensitivity appears to approach 100 percent. A recent comparison of the Roche Amplicor 1.5 DNA PCR with the Roche TaqMan viral load assay in South Africa found that the viral load method gave positive results at a younger age than did the DNA PCR in few patients,[68] an observation also made by others.[69]

There has been considerable interest in using dried blood spots (DBS) to handle specimens for viral load determinations in resource-limited settings where clinics are dispersed relative to laboratory services. Application of viral load assays on DBS for infant diagnosis has been evaluated. Using an inexpensive real-time RT PCR method for viral load (Generic Viral Load by Biocentric) there was complete concordance comparing plasma and DBS samples,[70] although the lower limit of detection with the DBS samples was 3,100 copies/ml, a level exceeded by most but not all infected 6 week old infants. Results from an adaptation of the Abbott m2000 viral load system for DBS samples from exposed infants was completely concordant with DNA PCR testing by the Roche Amplicor 1.5[71] on the same DBS. Qualitative RNA detection systems have been shown to perform well on DBS from exposed infants: 99 percent sensitive and 100 percent specific for the Gen-Probe Aptima HIV-1 RNA test as compared with viral load or DNA PCR on plasma or whole blood samples.[72] Adaptation of an automated total RNA plus DNA detection system (Roche Cobas AmpliPrep/TaqMan) to DBS yielded 99.7 percent sensitivity and 100 percent specificity on DBS for infant diagnosis, as compared with the more labor-intensive Amplicor 1.5 DNA PCR.[73] An evaluation of the Roche standard viral load assay (with a lower limit of quantitation of 400 copies/ml) was as or slightly more sensitive than DNA PCR in young infected infants, both being 96.2 percent sensitive in 4 to 6 week old infants and 100 percent sensitive after 7 weeks of age.[74]

Detection of viral antigen in plasma: Assays that detect the viral p24 antigen in serum were used in the past for assisting in making a diagnosis of infection in the newborn. However, sensitivity was low, and with the availability of more sensitive nucleic acid tests, p24 assays were abandoned. However, improved methods for p24 assay may yet prove useful in countries with limited resources or where nucleic acid tests cannot be performed reliably. Ultrasensitive (boosted) methods for p24 antigen detection, such as the TSA ELISA, have been reported to approach the sensitivity and specificity of nucleic acid assays.[75] The TSA method has been described elsewhere.[49] The p24 antigen assay is attractive because it is simpler to perform than nucleic acid test methods. When compared against nucleic acid sequence-based amplification of RNA for the diagnosis of HIV infection in infants the sensitivity of p24 detection in plasma was 91 to 95 percent, with the false-negative results coming from samples in very young infants with low viral loads.[76] Further, the use of dried blood spots as samples for p24 detection has been evaluated in several studies and reviewed by Cachafeiro.[77] However, the only evaluations for infant diagnosis included too few infected infants at the target age (6 weeks) for routine infant testing to determine the sensitivity with suitable precision.[77,78] The specificity of p24 methods has been very high in most studies. Although there have not been systematic comparisons of the sensitivity of p24 assay for different HIV-1 subtypes, studies have been done in several locales where expected differences in HIV-1 subtypes exist; there were no clear difference in results, as might be expected for this relatively conserved antigen. However, this needs to be further investigated.

Detection of reverse transcriptase activity in plasma: An alternative to nucleic acid and p24 antigen tests is the Exa Vir Load test (Cavidi AB, Uppsala, Sweden) that is similar to an ELISA. This is a quantitative test that detects reverse transcriptase (RT) activity in plasma. The test requires 2 to 3 days and an incubator, rocker, vacuum pump, and a

reader. The range of detection is 1 to 3,000 fg reverse transcriptase/ml plasma, equivalent to 200 to 600,000 copies/ml RNA copies, and the cost is low, making it attractive for resource-limited countries. The test has been shown to perform well as compared to PCR methods for viral loads.[79-82] The potential for infant diagnosis has not been thoroughly studied,[81] but in settings where this relatively simple, low-cost viral load method is in use and when other virologic methods for infant diagnosis are not available on a timely basis, it is an option that should be considered.

Detection of cell-associated virus-encoded DNA: Qualitative DNA PCR is still the preferred method by many healthcare providers for the diagnosis of HIV infection in infants. DNA PCR detects proviral DNA that has been integrated in the cellular DNA of the host. Peripheral blood mononuclear cells of the host are recovered from whole blood, DNA is extracted, and PCR is performed. The DNA PCR assay requires only a small volume of blood (which is important for newborn testing) and can detect minute quantities of HIV DNA in the newborn's blood. The method of DNA PCR has been described elsewhere.[49] Reported sensitivity for whole blood taken from infants 1 to 2 months of age who are subsequently proven to be infected have ranged from 90 to 100 percent (reviewed by Read,[48] see also Patton).[83]

Samples for HIV DNA detection may either be whole blood or dried blood spots. Multiple PCR methods have been used in various populations of exposed infants, making interpretation of test performance difficult because each method may yield slightly varying results. Several assay and patient characteristics are important to consider in assessing the performance of DNA PCR methods. Whole blood methods generally input larger blood volumes than DBS samples. The match between HIV-1 subtype and PCR primers is also critical, as are other methodologic details such as extraction methods from DBS samples. Earlier methods, such as the Roche Amplicor version 1.0 DNA PCR, were optimal for subtype B that is predominant in the United States. Investigators in the United Kingdom have found many samples from HIV infected infants and mothers[84] or infected children and adults[85] of diverse HIV-1 subtypes to produce false negative results with the Amplicor 1.0 method. A similar problem with undercounting or failing to detect HIV-1 RNA in nonsubtype B samples was seen with the Amplicor 1.0 viral load assay. However, the newer Amplicor 1.5 DNA and RNA PCR systems largely solved these limitations. In a study from South Africa,[86] where subtype C predominates, the Amplicor 1.5 DNA PCR on whole blood was 98.8 percent sensitive on a group of 58 infected 6-week old infants; the cause of the lone negative result in an infant later shown to be infected was unknown, although the authors point out that later transmission from unreported breastfeeding is a possibility. The same group evaluated the Amplicor 1.5 assay on venous DBS from 25 infected and 263 uninfected 6-week old infants and found 100 percent sensitivity and 98.8 percent specificity. Specicity was 100 percent when the sole false positive was tested on a repeat sample.[87] Similar results were obtained on a smaller number of DBS from capillary blood.[83] Another adaptation of the Amplicor 1.5 to DBS that detected viral DNA and RNA detected all 76 infants (mean age 9.4 weeks, range 1 day to 46 weeks) who were deemed to be infected by the NASBA viral load assay on plasma.[88]

In summary, the use of methods to detect viral RNA or DNA is invaluable for diagnosis of HIV infection in infants. DNA PCR on whole blood is the standard of care in resource-rich settings, and DNA PCR on dried blood spots is rapidly being implemented in resource-limited settings. However, other virologic methods may be considered depending on local resources and demonstration of operational utility. Table 1.2.3 lists the types of serologic and virologic assays. The use of these assays in diagnostic strategies is discussed in the section below.

Strategies for Diagnosis of HIV Exposed Infants

The development of a strategy for the early diagnosis of HIV infection in exposed infants depends on several factors, including the resources available, interventions

Table 1.2.3: Serologic and virologic testing methods

Serologic screening tests
ELISA
Rapid Tests
Agglutination (simple test)
Serologic supplemental (Confirmatory) tests
Western blot
Indirect Immunofluorescence assay (IFA)
Line Immuno Assay (InnoLia)
Rapid tests (second, different rapid test to confirm screening rapid test)
Virologic methods
RNA detection
Quantitative
Reverse-transcribed PCR; Real-time PCR
NASBA
bDNA
Qualitative
Aptima (for diagnostic purposes)
HIV p24 antigen assay

that affect transmission and breastfeeding duration. Presented here are strategies that apply to resource-rich settings (where formula is provided, the risks of substitute feeding are minimal, and the cost of testing is not a major factor) and strategies for resource-limited settings (where some proportion of HIV exposed infants are breastfed and testing costs must be minimized).

Testing strategy for the exposed infant in a resource-rich setting with universal substitute feeding of HIV exposed infants: For the nonbreastfeeding population of HIV exposed infants in the United States, the American Academy of Pediatrics recommends virologic testing at 0 to 14 days, 1 to 2 months, and 3 to 6 months of age.[48] At the University of Maryland, DNA PCR is performed at birth, 1 month, 2 months, and 4 months of age. Infants exhibiting at least 2 negative PCR results after 1 month of age including one after 4 months of age are declared definitively uninfected and no further testing is required. If a virologic test is positive, it should immediately be repeated; a second positive result is definitive. Criteria for presumptive and definitive diagnosis and exclusion have been defined[48] as:

Presumptive exclusion of HIV-1 infection can be based on: (a) 2 negative virologic test results (one obtained at ≥2 weeks and one obtained at ≥4 weeks of age), or (b) 1 negative virologic test result obtained at ≥8 weeks of age, or (c) 1 negative HIV-1 antibody test result obtained at ≥ 6 months of age.

Definitive exclusion of HIV-1 infection is based on: (a) 2 negative virologic test results (one obtained at ≥1 month of age and one obtained at ≥4 months of age) or (b) two negative HIV-1 antibody test results from separate specimens obtained at ≥6 months of age.

Discrepant results or negative results in the face of highly suggestive symptoms should be further investigated. In the resource-rich setting, the turnaround time for results is usually fast enough to have confirmatory results reported before initiating therapy, but if there is any delay, antiretroviral therapy should be started. Using these strategies and reliable virologic methods, confirmatory serology at 18 months of age for infants who have met criteria for definitive exclusion of HIV infection may be omitted.[89]

Testing strategy in the resource-limited setting where some or all infants are breastfed: In a presumably non-breastfeeding population in a resource-limited setting, a single positive virologic test at 6 weeks should capture all infants infected during pregnancy and delivery in time to intervene with antiretroviral therapy before death or before irreversible damage occurs. Missed diagnoses would occur only if there is laboratory error or, as is more common, if there is a mistake in assigning samples and results to the correct patient. However, the presumption that an HIV exposed infant is not breastfeeding in a setting where most infants do breastfeed is often incorrect. Additionally, where some or most HIV exposed infants will be breastfeeding, it is difficult to have separate diagnostic approaches for breastfeeding and non breastfeeding infants.

The timing of the first test must be in concert with the sensitivity of detection, allowing sufficient time for infants infected during delivery to develop detectable virus, versus the urgency to initiate antiretroviral therapy in infected infants, a process that may be delayed by a number of circumstances. As reviewed above, virologic assays approach 100 percent sensitivity by 6 weeks of age. Extensive experience with certain commercial DNA PCR kits allows for greater confidence than do reports of using various custom methods that have been evaluated on only a relatively small number of infants. An analysis of the optimal timing of a single virologic test using data from South Africa suggested an age of 4 to 6 weeks.[90] In order to facilitate adherence to testing, it is best to combine testing with another event such as a vaccination visit; the 6 week point for routine infant vaccines is convenient. Additionally, the later that testing is scheduled, the less likely it will happen.

Developing a strategy for the timing and methods for follow up testing of the infant with ongoing risk of infection while breastfeeding is more difficult, given the constraints against doing frequent serial virologic tests. An appropriately timed rapid serologic test is potentially a simple, rapid, and inexpensive method for screening infants to determine the need for a virologic test. For the breastfeeding (or possibly breastfeeding) infant whose PCR at 6 weeks of age was negative, waiting until 18 months of age to do a serologic test is too long because of the increased mortality in breastfeeding acquired infection seen after about 7 months of age. Alternatively, the earlier repeat testing is done during breastfeeding, the more likely it is that maternal antibody will be detected or that later breast milk transmission will be missed, and later lower the specificity of serologic testing and the less valuable this. A reasonable compromise is to do a screening serologic test at 9 months of age. As summarized in Table 1.2.1, the proportion of uninfected, exposed infants who will test positive at this point depends on the sensitivity of the test employed. Infants testing positive by a rapid test should have a sample for repeat virologic test obtained the same day.

It should be recognized that there are no clear data on how quickly an infant infected from breast milk mounts an antibody response; it is often presumed to be within 3 months, by extrapolation from studies in adults. It is also not known how long it takes the late-infected infant to have enough virus to be detected by virologic methods, although extrapolation from newborns and adults suggests that, with sensitive techniques, providers can rely on late-

infected infants to have detectable virus by 6 weeks after infection. Whether this may be modified by maternal HAART (which exposes the infant to low levels of antiretrovirals that vary with different drugs) or daily infant nevirapine, may be suspected but is not known. Because of delays in mounting an antibody response, the possibility of transmission later in breastfeeding, and the uncertainty in the timing of the last exposure to breast milk, the infant who is seronegative at 9 months should not be declared definitively uninfected, even if weaned at some earlier point. An appropriate time for repeat serology is 18 months of age. At that time, all or all but a small fraction of exposed, uninfected infants should have seroreverted, depending on the sensitivity of the serologic test employed. Asymptomatic infants who are seronegative at this time and reliably have not breastfed in the past 3 months can be declared definitively not infected. Infants who are seropositive at 18 months should be presumed to be infected. However, if a highly sensitive serologic test is being used, then the possibility of late seroreversion should be considered. By performing two different rapid tests at 18 months of age (either in parallel or sequentially), as is the practice in most programs for adults and children, the risk of a false-positive result is reduced. In addition to residual maternal antibody, some proportion of uninfected adults and children will be reactive on a single screening serology, hence the importance of a second, more specific serologic test (Western blot or second rapid test that has validated specificity). Because there are many variables that contribute to making an accurate diagnosis, programs should monitor performance by doing DNA PCR on at least a subset of children seropositive at 18 months of age to determine if the serologies are correct.

Other risk factors should be considered when interpreting test results, including whether there has been adequate antiretroviral prophylaxis, or whether there are suggestive clinical symptoms. If there is doubt, a virologic test should be performed for confirmation, while preparations for initiating antiretroviral therapy are begun. Such cases are unusual and will not significantly increase the virologic testing workload, but if thoroughly investigated will contribute to confidence in the testing system. An analysis using data from Uganda on the cost-effectiveness of performing a screening serologic test on infants known to be exposed before doing a DNA PCR found cost savings for infants >3 months of age. There was some loss of sensitivity in this model, showing a 94.3 percent sensitivity if DNA PCR were performed on all exposed infants from 3 months to 18 months of age, and an 87.8 percent sensitivity if a single rapid serologic test was done first and DNA PCR were done only if the serology was positive.[55]

The child who is seronegative at 18 months is not necessarily uninfected, particularly if there is ongoing breastfeeding or any exposure to breast milk within the past 3 months. In such cases, serologic testing should be repeated 3 months after all exposure to breast milk has ceased. Because of data that strongly support the effectiveness of maternal HAART or daily infant NVP for prevention of breast milk transmission, a wider appreciation of the dangers of early weaning, and the strong cultural impetus for prolonged breastfeeding in many settings, infants may require HIV testing until 24 months of age or older. The need for continued monitoring for infection, prolonged maternal HAART or daily infant NVP for prophylaxis against infection, prolonged cotrimoxazole prophylaxis, and vigilance against malnutrition due to premature weaning or inappropriate complementary or weaning feeds means that the HIV exposed infant requires a coordinated, focused package of services applied on a longitudinal basis, very much like antiretroviral therapy of the infected child or adult. Programs must recognize that this paradigm is not just a minor addition to routine child healthcare or routine HIV care, but requires a distinct set of skills and resources and better integration of child health and HIV services.

All positive virologic test results should be confirmed with a second sample obtained as soon as possible. Because the large majority of tested infants will be uninfected, the performance of a second, confirmatory test or strategy should not overburden the testing system. Diagnostic certainty is critical for diagnosis, for the family, and to ensure quality of the results. Treatment of the infected infant is a matter of urgency regardless of the infant's apparent good health; initiation of antiretroviral therapy should not be delayed while awaiting confirmation of the diagnosis.

Figure 1.2.2 depicts a testing algorithm promoted by the University of Maryland School of Medicine and Institute for Human Virology for the Multi-country AIDS Relief Program. Key points are that: (a) the exposure status of all infants must be known, (b) repeat serology should be done at 9 and 18 months and 3 months after weaning (with reflex to PCR if serology is positive before 18 months of age), (c) any symptomatic infant should promptly be tested, and (d) seronegative infants with suspicious symptoms should have virologic testing to rule out seronegative HIV infection. Modifications to the algorithm may be considered if greater resources permit. Examples might include performing PCR at birth (especially for infants whose mothers did not get adequate antiretroviral treatment during pregnancy) or, in settings where breastfeeding is the norm, doing a PCR at 9 months of age on all infants. Where breastfeeding of exposed infants is not practiced, a repeat virologic test at 4 months is indicated.

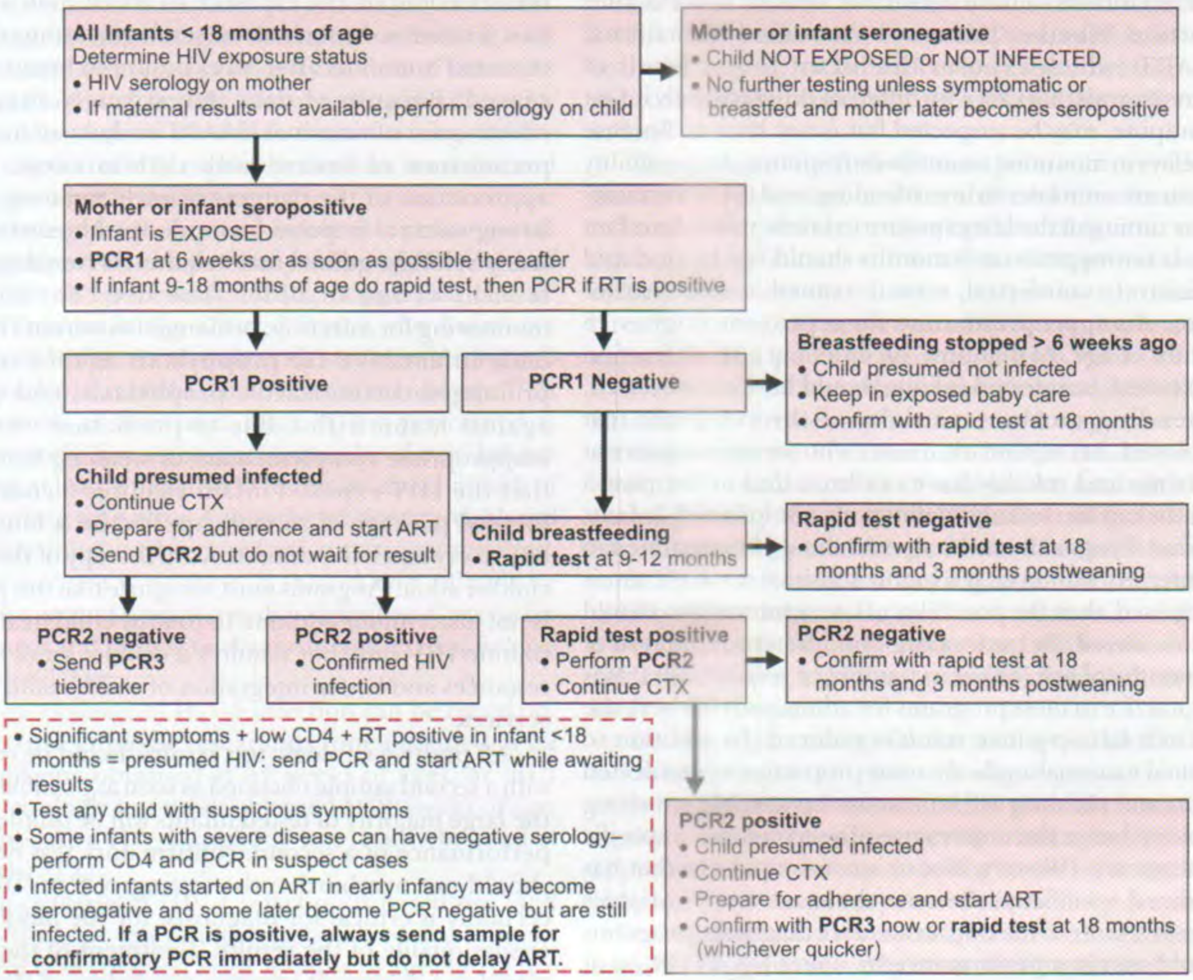


Fig. 1.2.2: HIV diagnostic approach in infants <18 months of age if DNA PCR available (University of Maryland school of medicine-institute of human virology AIDS relief version data 3 December, 2009)

Care to Ensure that Infected Infants are Promptly Treated

Comprehensive maternal-infant HIV care requires a long sequence of events, starting from the diagnosis of concurrent pregnancy with HIV infection and continuing through maternal evaluation and antiretroviral therapy, to protection of the breastfeeding infant with maternal HAART or daily infant nevirapine, to monitoring for growth, nutrition, and survival of the infant to HIV testing of the exposed infant, and through initiation of antiretroviral therapy in infected infants. Despite the availability of effective interventions, many mother-infant pairs drop out of the process at various steps. This drop out rate cumulatively weakens the effectiveness of maternal-infant HIV care and is commonly referred to as the "PMTCT cascade".[91-93] The final steps of matching diagnostic results with the infected infant and initiating HAART (as is now recommended by the WHO for all infected children under 2 years of age) often represent major drops in the cascade. Indeed, in Swaziland, only 19 percent of infants with positive results in the national early infant diagnosis program could be verified to be on antiretroviral therapy.[92] In Lilongwe, Malawi, of 746 infants with positive results in the laboratory, only 146 were in HIV care. These children were diagnosed at a median age of 89 days of life, yet did not get to the pediatric treatment center until a median age of 158 days, by which time 26.7 percent had WHO stage 3 or 4 disease; many of the children died.[94] A representative national survey in Uganda found that although the laboratory could turn results out fairly quickly (<30 days), the infants were not having samples drawn until an average age of 6 months, and 43 percent of families never received results.[95]

Essential to shoring up these drops in the cascade and making HIV testing of the infant of benefit are maintenance of a database, accessible to the site, of all HIV infected pregnant women and their infants. There often are strong cultural barriers to follow up of the HIV infected woman and her infant after delivery. Keys to getting past these barriers include early engagement of male partners, a family-friendly environment in the clinic, and extension of clinic services into the community, especially community workers who can make discrete home visits to persuade a woman to remain engaged in care.

Testing of the Older Child

Although the technical considerations for testing of children beyond the first two years of life are very similar to testing in adults, there are important considerations unique for children. When testing most children over about 18 months of age an ELISA or rapid test, followed by a supplemental test such as the Western blot, is a sensitive and specific strategy for diagnosis. In settings where rapid tests are used but supplemental tests may not be available, a test strategy using two rapid tests is recommended. However, the tests must be chosen carefully, with the initial test being highly sensitive, followed by a different rapid test that has been validated to be specific (similar to using a confirmatory test). The two tests should be from different manufacturers, of different principle (e.g. flow-through versus lateral flow), and/or ones that have different antigens for detection of antibodies.[49] This two-test strategy has been validated in many populations and, if used correctly, is preferred over a single rapid test which may not result in adequate specificity, particularly in a low-prevalence population.

Just as all adults should know their HIV status, the HIV exposure or infection status of all children should be known. Strategies for accomplishing this must be prioritized according to the expected yield of infected children. The starting point is the testing of children of infected women. If an infected woman was documented to be seronegative at some point, then any child born or breastfed afterwards (or to be more conservative, after the date 3 months before the mother's negative test to account for the window period for her seroconversion) should be tested, regardless of apparent well-being. Complete case-finding among potentially exposed children is best accomplished by recording prominently in the mother's record, the age, testing status, test results, and care status of all her children in addition to her sexual partner(s). This record should periodically be reviewed for completeness. This author (DW) has on more than one occasion cared for a child with HIV infection for years only to be later presented with a sibling with advanced disease who somehow escaped earlier testing.

Parents often are hesitant to test older children, expressing doubt that an apparently well child is infected. Much of this reluctance is likely due to their own experience with testing: they recall receiving detailed pre- and post test counseling regarding HIV, disclosing their sexual practices, and so on. A culturally and developmentally appropriate balance must be reached between respecting the parent's right to privacy and respect for the child's autonomy, versus the duty to protect the child from untreated HIV infection. Systems need to be in place to allow for discussion of the testing of children to occur in private with the parent(s) alone and then to obtain blood from the children without disclosing the parent's status. Disclosure of his or her diagnosis to the infected child is an important part of the care of children with HIV infection, but is best accomplished as a process over time, in concert with the parents. Questions regarding the degree to which the parent is the proper guardian of the child's autonomy, or the child should speak for him/herself, or when the clinician must act to protect the child at the risk of offending the parent's sensibilities are common to the practice of pediatrics.

How old is too old to require HIV testing in order to rule out HIV infection in the potentially exposed child? The grim statistics on the health and survival of HIV infected children often obscure the fact that a minority of congenitally infected children survive many years or even into adulthood without being diagnosed. Simply put, before a child is too old to have survived congenital HIV infection, he or she is old enough to acquire HIV infection sexually. Advising families on testing the adolescent who potentially was exposed as an infant must be individualized. In some cases, the family may know or suspect that the adolescent is sexually active and testing can be strongly encouraged on that basis. In other instances, the parent may be able to disclose to the adolescent, information about the parent's infection status which may already be known or suspected by the adolescent, thereby, indicating the need for the adolescent to be tested. However, the younger adolescent can be tested without disclosing the purpose of testing.

Settings where there is a relatively high prevalence of pediatric HIV infection include general clinics, tuberculosis clinics, and malnutrition clinics, as well as hospital wards. In many settings, all hospitalized children are routinely tested for HIV infection, usually on an "opt-out" basis. If there is good documentation of the mother's sero-negative status, testing is not necessary. Because HIV is a major cause of death of young women, all orphans should be tested, regardless of a family's perceptions about the mother's cause of death. Any child with symptoms of HIV infection should be tested, regardless of maternal history. Such histories may be misleading; the mother may have been infected during pregnancy or lactation but after

antenatal testing, or the child may have acquired HIV from blood transfusion, unsterile medical tools or other practices such as scarification or tattooing, or even from abuse. Finally, the vaccination clinic is an appropriate site to screen for HIV exposure. Vaccine/growth cards should discretely indicate an infant's HIV exposure status. When the mother has not been tested during pregnancy, either the mother or the infant or child should be tested in the clinic. In areas of very high HIV prevalence, testing of all children receiving routine preventive health services has been found to be an effective use of resources.

Pitfalls in the Diagnosis of HIV in Infants and Children

An emerging problem arising from the availability of early infant diagnosis and antiretroviral therapy is the effect of HAART on diagnostic test results. The majority of infants starting HAART in early infancy do not develop an antibody response to HIV. [96-98] If such an infant has a "routine" serology done at 18 months or so, the clinician may mistakenly think that the child's initial diagnosis was incorrect because false negative results have occurred. This

Clear definitions of Infant HIV status will lead to appropriate management

The terms "HIV-positive" and "HIV-negative" are vague and confusing when applied to infants and children. The words "positive" and "negative" are best applied to results of a specified test, not to the child. There are several categories into which a child's HIV status may be classified. Clearly identifying which applies to a child will direct appropriate evaluation and treatment and keep the family informed. Below are some definitions of patient status:

HIV exposed: An infant or child of any age whose mother is known to have been infected with HIV at any time during pregnancy or lactation.

HIV exposure status unknown: An infant or child whose exposure status is not known. Although India ranks number 10 in the world for number of HIV infected young women (and is the only non-African country in the top 20), only about 20 percent of pregnant women were tested for HIV, as of 2008. So the large majority of Indian infants and children are "exposure status unknown".

HIV-exposed, presumptively not infected: The mother is known to have HIV infection and the child has 1 negative virologic test done 6 weeks or more after birth or cessation of breastfeeding or one negative serology after 6 months of age and more than 3 months after cessation of breastfeeding.

HIV-exposed, definitively not infected: The mother is known to have HIV infection and the child was conclusively shown not to be infected after the end of the incubation or window period, as measured from last time of exposure; e.g. a non-breastfed infant with two negative PCR tests (one after one month and one after 4 months of age) or a negative PCR at 6 weeks and a negative serology.

HIV-exposed, presumed not infected, exposure continuing: An infant of an HIV infected mother who has had a negative HIV test, such as a negative PCR for HIV DNA at 6 weeks of age, but has continuing exposure to breast milk. A negative virologic test at more than 6 weeks or a negative serologic test more than 3 months after the last exposure to breast milk is presumptive evidence against transmission from breastfeeding.

Presumed HIV infection: A child with a positive serologic test prior to the point at which maternal antibodies should be undetectable and symptoms are strongly suggestive of HIV, perhaps supported by a low CD4 percent, but in the absence of virologic testing.

HIV infected, unconfirmed: A child with one positive virologic test for HIV or one positive serologic test* after the point at which maternal antibodies should be undetectable.

HIV infected, definitive: A child with 2 positive virologic tests for HIV or 2 positive serologic tests* after the point at which maternal antibodies should be undetectable.

*An ELISA or single rapid test is not specific enough to diagnose HIV infection. A definitive serologic diagnosis requires either a diagnostic Western blot (2 or more critical bands) or, in a resource-limited setting, a positive result on 2 different rapid tests. The specificity of such a rapid test algorithm must be validated against Western blot results on a large number of samples from that region.

Testing a test: measuring the clinical utility of a test

A test for a disease has characteristics intrinsic to the test, the sensitivity and specificity. However, the clinical usefulness of a test also depends on how commonly the disease is present, i.e. its prevalence. Clinical utility is described by the positive predictive value and negative predictive value, which depend on the sensitivity and specificity of the test and on the prevalence in the population.

Sensitivity: The proportion of people with the disease that have a positive test result.

Specificity: The proportion of people without the disease that have a negative test result.

Positive predictive value: The proportion of positive test results that are from people with the disease, i.e. (true positive)/(true positive + false positive).

Negative predictive value: The proportion of negative results that are from people without the disease, i.e. (true negative) /(true negative + false negative).

A test may be useful if a disease is common, but less useful if the disease is rare *in the population being tested*. For example, if a test for HIV has 95 percent sensitivity and 95 percent specificity and 20 percent of the tested infants are infected, then the positive predictive value is 0.83, which means that 17 percent of infants with a positive test do not have HIV. Similarly, if the same test is used among a group of infants of which only 2 percent are actually infected, then the positive predictive is only 0.28. If a test with 99 percent specificity is used, however, the positive predictive value would improve to 0.67—an improvement, but 33 percent of positive results would still be false-positives. The positive predictive value in this example does not exceed 90 percent until the specificity of the test reaches 99.8 percent. So among infants (such as infants of mothers who were taking HAART) where HIV is rare, the specificity of the test must be very high.

Because false-positive PCR results are usually the result of sample mislabeling or contamination (errors not inherent to the patient or method), repeating positive PCR testing on a second sample greatly increases the specificity of an early infant diagnosis program.

is especially a problem if the infant was presumptively diagnosed based on serology, clinical symptoms, or CD4 count. Not only can the serology be negative in the infected child who initiated HAART in early infancy, but so can an ultrasensitive viral load, DNA PCR, viral culture, and tests for cellular response to HIV antigens, even in a child whose infection was unequivocally established in infancy.[96] This leaves the clinician with no means of confirming a diagnosis (short of stopping therapy and retesting, which is not adviced). It is imperative, then, that the diagnosis of HIV infection be established as securely as possible in infants. Treatment cannot be delayed in suspect cases, but where there is not a rapid turnaround time for virologic testing results, a sample for confirmatory testing should be obtained and assessed. If conflicting results are subsequently found (e.g. a first PCR positive, but confirmatory sample negative), a third sample should be obtained immediately. A DNA PCR on that sample should be positive for at least a few months after starting therapy, even if the viral load has rapidly become undetectable (as it should within 3-6 months of initiating HAART).

Because infected, early treated infants commonly serorevert, serology at 18 months is not recommended for the infant whose infection status was clearly established with positive virologic tests on two occasions. For example, in an African child seen by one of the authors (DW), 2 early DNA PCR results on DBS were positive and HAART was started by 3 months of age. Viral load assays, first done several months later, all exhibited undetectable results. A rapid serologic test and DNA PCR on a dried blood spot performed at about 18 months of age were negative. However, a DNA PCR subsequently performed on whole blood, using a larger input volume than with the DBS, was positive. As long as there is a robust, quality-assured testing system that rapidly delivers results, and infected infants are rapidly retrieved for a second sample and initiation of HAART, there should be no doubt regarding the child's status. A recent survey of PCR positive children reported many infected, treated children were seronegative by rapid serologic tests.[99]

Infected children can be seronegative in other circumstances. Some infected infants will transiently lose maternal antibody before becoming seropositive.[54,62] Others, particularly with rapidly progressive disease, fail to seroconvert. For example, a seronegative child with symptoms strongly suggestive of HIV infection, including depressed CD4 count, should have a virologic test for HIV, particularly if it can be established that the mother is infected. Although commonly seen in early-treated infants, children initiating HAART at an older age can, after many years of fully suppressive HAART, lose antibodies to HIV, as has been described in adults.[99]

Case Study

Case : A Diagnostic Dilemma

A 20-month-old child from Kenya was evaluated for HIV infection after exposure from an HIV infected mother and was evaluated at the University of Maryland (unpublished). The mother was PCR positive for HIV RNA, and was treated for 3 months at which time the viral load became negative (undetected) for viral RNA. The infant was antibody positive with a very high titer of antibodies to HIV, but the Western blot was completely negative (which is unusual in infected persons with high antibody titer). HIV-2 testing was not performed because the quantity of plasma was insufficient. There was no follow-up after 5 months because the mother and child did not return for follow-up testing. Although not resolved, this case can be used to raise questions as to what else could be done or what should be done if the child returns. First, it may not be possible to determine if the child is infected unless he returns. Some possibilities that should be considered in this case are: (1) it is possible that the infant was infected with a subtype of HIV that may not be detected by the NAT that was used (the child was from Africa where HIV non-B viral types exist). It is recognized that not all NAT can detect all HIV-1 Group M clades,[100] and most cannot detect HIV-1 group O or HIV-2. If sufficient plasma is available, it might be possible to test for these HIV variants through serologic or NATs. In fact, a new test just marketed is the Abbott Real-Time HIV-1 nucleic acid test that has an increased ability to detect all HIV-1 variants (all groups and subtypes), and other more sensitive NATs may detect infection.[101] Also, these ultrasensitive NATs have sensitivities of 20 to 40 RNA copies/ml, and therefore may be more sensitive than other NATs for detecting low levels of viral RNA that may occur with viral variants and during treatment (the mother was treated); and (2) a comparison of specific antibody profiles (by Western blot) could be made to determine if the mother and the child have different "qualitative" profiles of bands. If significantly different (e.g. presence of an additional band on one of the samples), it could be suggested that the infant is infected. The most definitive resolution of this case would be accomplished if a new specimen were received from the infant (if he returns). In such case (months after the initial testing), antibody and NAT testing would be effective to arrive at a correct diagnosis. This case study exemplifies the importance of having a good means to minimize the loss to follow-up of cases that are not resolved.

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1.3

Natural History of HIV in Children

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Introduction

Over 2 million children are infected with the human immunodeficiency virus (HIV) worldwide. In Asia, there are over 200,000 HIV infected children who are between 0 to 14 years making up 4 percent of the total HIV population. The natural history of HIV infection in children differs from adults with a more rapid progression of disease. This is due to the impact of the virus on an immature developing immune system, and subsequent effect of on-going viral replication and inflammation on somatic and neuro developmental growth. In the young child, the opportunistic infections that result from immune deficiency are often primary, not reactivation disease, creating greater morbidity. Despite these issues, the evolution of therapy for HIV infection in children has greatly impacted disease progression and the robust immune capacity seen in children brings promise for continued improvement in survival and quality of life.

The cases given at the end of this chapter illustrate some important points regarding the natural history of HIV in children.

HIV Progression in the First Year of Life

The challenges of HIV presenting in the first year of life reinforce the need for prenatal counseling and HIV testing of all pregnant women so that maternal HIV prophylaxis can occur. More than 80 percent of pediatric HIV is due to maternal-to-child transmission. Transfusion acquired disease still occurs in areas which have issues with blood safety and often impacts children with requirements for multiple transfusions such as thalassemia. Usually, HIV infected neonates are asymptomatic, although a number of perinatal conditions may occur because of other maternal comorbidities. These include prematurity and small birth weight, fetal alcohol syndrome, opioid withdrawal, anemia and other perinatal infections, including congenital syphilis, CMV, HBV, and HCV. There is no acute HIV syndrome recognized in vertically infected infants as seen in adults or behaviorally infected adolescents. Ideally, infants exposed to HIV should be tested with nucleic acid testing before symptoms occur. HIV infected infants often present with chronic diarrhea, oral candidiasis, failure to thrive and respiratory symptoms. Early central nervous system findings include loss or delay in motor skills, irritability and poor head growth.

There is a bimodal distribution to the presentation of HIV in children. In the US and Europe, prior to widespread use of antiretrovirals in infants, an estimated 10 to 20 percent of infants presented with early symptoms of AIDS and death in the first two years of life.[1] These rapid progressors often presented with failure to thrive, oral candidiasis, pneumonia and encephalopathy. *Pneumocystis jiroveci* pneumonia (PCP) was the most common presenting opportunistic infection in infants before routine HIV prenatal testing programs were established and trimethoprim-sulfamethoxazole prophylaxis was introduced. Infants who developed PCP such as the infant presented in case 1, had dismal survival rates in the first year.[2] Early presentation of disease is associated with *in utero* transmission of HIV, advanced maternal disease and high maternal viral burden.[1,3,4] The challenge of HIV in infancy is that there is no standardized method to identify which infant will become a rapid progressor. Infants have naturally high CD4 counts and it is important to review age appropriate normal values when interpreting. Also, if available, CD4 percentages in children under 5 years have less variability and therefore are often used to follow progression. The risk of progression is greatest in the first year of life and CD4 counts and viral loads are poorly predictive of progression of disease. At any given CD4 count, infants less than 12 months are more likely to progress to AIDS.[5]

A similar bimodal distribution occurs in resource limited settings; however, as many as 50 percent of infants will present with early symptoms and die in the first two years of life.[1,6] Early onset symptoms such as failure to thrive and diarrhea are often associated with subsequent

death or continued progression.[6] The most common causes of death are diarrheal illness or pneumonia. In a study from Zaire, persistent diarrhea had eleven times the risk of death in HIV infected infants compared to an HIV uninfected population.[7] Cotrimoxizole prophylaxis has efficacy in untreated HIV infected infants in preventing some infectious illness.[8] In TB endemic areas, coinfection with tuberculosis occurs in 30 to 50 percent of cases of HIV infection and contributes to morbidity and mortality.[1] Figure 1.3.1 depicts the cycle of viremia, inflammation and immune dysregulation that drives progression in infants.

There is strong and consistent data to suggest that HIV infected infants benefit from early antiretroviral therapy. The risk of progression is greatest in the first year of life and CD4 counts and viral loads are less predictive of progression of disease. As stated previously, pooled analysis of multiple studies show that at any given CD4 count, infants less than 12 months are more likely to progress to AIDS.[5] HIV viral loads rise quickly in the first few months of life and remain quite high for the first year. These high values can occur in both progressors and infants who do not progress hence they are not strongly predictive unless associated with low CD4 counts. The CHER study conducted in South Africa randomized asymptomatic infants to receive antiretroviral therapy beginning at 12 weeks of age versus waiting for decline in CD4 or clinical symptoms. Early treatment was associated with a 76 percent decrease in death and a 75 percent decrease in progression to AIDS. In the CHER study, infants often died from their first clinical event which was most likely gastroenteritis or pneumonia.[9] This highlights the need for close follow-up of exposed infants, early HIV testing and prompt access to antiretroviral therapy. There are several additional cohort and observational studies which showed similar efficacy and good response to therapy in infants.[10] Based on the strength of the data, the WHO will now recommend that all HIV positive infants under 2 years of age be treated regardless of CD4 count or symptoms.[11, 12]

The child described in case 1 is a classic example of a rapid progressor who when untreated, has a poor prognosis. In addition to supportive care and treatment for PCP, the key step is to initiate antiretroviral therapy. Even with HAART, she has an uncertain future. In multiple studies, children who start antiretrovirals while asymptomatic are much more likely to survive after five years compared to children with CDC Category C disease who start treatment.[13]

HIV Progression after the First Year of Life

HIV disease progresses less rapidly after the first two years and more slowly after 5 years of age. In older children, CD4 count and viral load have better predictive value and are independent predictors of disease progression.[14, 15] Children who are missed in the perinatal period due to lack of maternal diagnosis during pregnancy and who do not die in the first two years often present between 36 and 60 months of age. In a systematic review of multiple studies from India, the mean age of presentation was 4 years.[16] The most common presenting symptoms are presented in Table 1.3.1. Recurrent and acute respiratory infections are a common presentation with a broad differential. Over 60 percent of children infected with HIV will continue to have recurrent respiratory infections.[17] These children have increased susceptibility to bacterial pathogens such as *streptococcus pneumoniae* and *haemophilus*, in addition to more prolonged viral respiratory diseases. In some series in high endemic areas, tuberculosis was present in 30 to 50 percent of cases at diagnosis and was the most common opportunistic infection.[18,19] Both pulmonary and extrapulmonary disease was seen. The treatment of TB complicates initiation of antiretroviral therapy due to the issue of immune reconstitution inflammatory syndrome (IRIS) as well as drug interactions between anti TB and antiretroviral therapy. The WHO recommends initiation of HAART within 8 weeks after starting anti-TB therapy and this is further discussed in the chapter on HIV and lung diseases in children. Lymphoid Interstitial pneumonitis (LIP) may mimic tuberculosis in symptoms and X-ray findings. LIP can present with chronic cough, tachypnea, clubbing and interstitial reticulonodular infiltrates on CXR. This can result in pulmonary hypertentions. LIP has been associated with good prognosis of HIV disease.[2,6]

Other poor prognostic clinical presentations include malnutrition, encephalopathy, anemia, and chronic diarrhea. Stage 4 WHO criteria and CDC Category C diagnoses are all associated with poorer prognosis. In an Italian cohort of perinatally infected children, 44 percent

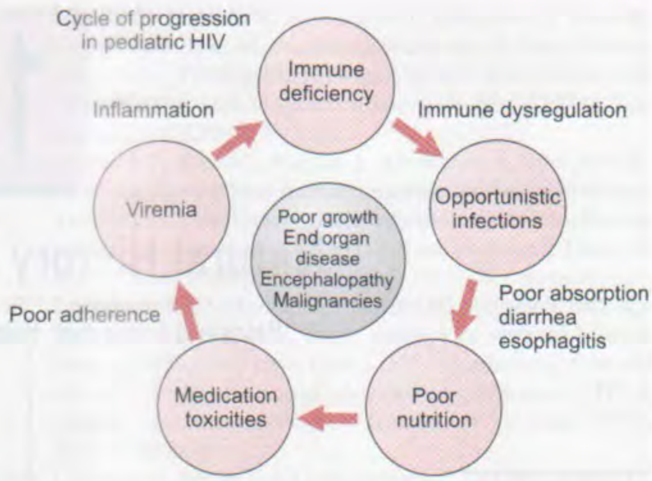


Fig. 1.3.1: Pathogenesis of HIV progression

Table 1.3.1: Clinical manifestations of pediatric HIV at the time of diagnosis

Fever	30-60%
Lymphadenopathy	40%
Hepatosplenomegaly	40-70%
Anemia	40-50%
Failure to thrive	50-70%
Diarrhea	20-30%
CNS involvement	5-15%
TB co-infection	30-50%
Candidiasis	20%

Source: Table adapted from Singh, H 2008. Pooled information from both inpatient and outpatient studies.

of the children who were diagnosed with a category C disease died within one year.[20] As expected CDC Category A had the best survival, 62 percent at 8 years in this group with mixed exposure to antiretroviral therapy.

In addition to clinical staging, an important component of assessing a child's individual risk and need for treatment is the CD4 count and HIV viral load. As stated previously, both are independent predictors of progression and risk of death; however, a CD4 count of less than 15 percent has stronger prognostic value than high viral load.[14] There is variability in CD4 measurements; it is recommended that if possible, CD4 percentage be used in the first five years of life.[21] The CD4 can be greatly influenced by acute illness, therefore it should be measured when the child is clinically stable. The Pediatric Prognostic Markers Collaborative Study pooled longitudinal data from multiple cohorts in US and Europe; Table 1.3.2 depicts death and AIDS/death rate per 100 person-years by current absolute CD4 count and age in HIV infected children who had received no therapy or only zidovidine monotherapy. Investigators demonstrated the poor reliability of absolute CD4 in infancy and also showed that after 5 years of age, there are similar rates of progression to AIDS between children and adults with same CD4 count.[5] Similar to adults, when the CD4 falls to 200 cells /ml, the risk of progression to AIDS rises to 4 percent per year. In resource limited settings, the total lymphocyte count can also be used and has predictive value just slightly less than CD4 counts. Over 12 months of age, rates of AIDS and death increased significantly at total lymphocyte values <1500 to 2000 cells/ml.[22] A risk calculator based on data from the HIV Pediatric Prognostic Markers Collaborative Study (HPPMCS) can be used to derive estimates of individual patient's risk of progression to AIDS or death based on age plus CD4 count, lymphocyte count or viral load.[23] Table 1.3.3 is derived from early data on an NIH sponsored intravenous immunoglobulin therapy trial in US children. It demonstrates the association between HIV RNA copy number and CD4 count with long term risk of death.

Table 1.3.2: Death and AIDS/death rate per 100 person-years by current absolute CD4 count and age in HIV infected children receiving no therapy or Zidovudine monotherapy*

	Absolute CD4 cell count (cells/mm^3)					
Age (years)	*< 50*	*50-99*	*100-199*	*200-349*	*350-499*	*500+*
	Rate of death per 100 patients-years					
0-4	59.3	39.6	25.4	11.1	10.0	3.5
5-14	59.3	39.6	25.4	11.1	10.0	3.5
	Rate of AIDS or death per 100 patient-years					
0-4	82.4	83.2	57.3	21.4	20.7	14.5
5-14	64.3	19.6	16.0	6.1	4.4	3.5

*Modified from HIV Paediatric Prognostic Markers Collaborative Study and the CASCADE Collaboration. J Infect Dis 2008. AIDSinfoNIH, www.aidsinfo.gov.

Table 1.3.3: Association of baseline human immunodeficiency virus (HIV) RNA copy number and CD4+ T cell percentage with long-term risk for death in HIV infected children*

Baseline HIV/RNA§ copies/ml/baseline CD4+ T cell percentage	*No. of patients¶*	*Deaths†*	
		No.	*(%)*
≤ 100,000			
≥ 15%	103	15	(15%)
< 15%	24	15	(63%)
> 100,000			
≥ 15%	89	32	(36%)
< 15%	36	29	(81%)

*Data from the National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial.

†Mean follow-up: 5.1 years.

§Tested by NASBA® assay (manufactured by Organon Teknika, Durham, North Carolina) on frozen stored serum.

¶Mean age: 3.4 years.

Source: Mofenson LM, Korelitz J, Meyer WA, et al. The relationship between serum human immunodeficiency virus type 1 (HIV-1) RNA level, CD4 lymphocyte percent, and long-term mortality risk in HIV-1 infected children. J Infect Dis, 1997;175(5): 1029-30 and from www.aidsinfo.gov.

Slow-Progressors—Late Presentation of HIV

Children with pediatric HIV can present later in the first or even in the second decade and may not have a long history of previous illnesses (see case 3). These patients can be diagnostic challenges presenting with immune thrombocytopenic purpura, anemia, recurrent parotitis, chronic diarrhea, cardiomyopathy, encephalopathy, or stroke. There may be clues in the family history which helps to indicate HIV risk factors such as mother's death.

These patients are slow progressors, also referred to as long term non progressors (LTNP) in the literature. LTNP are a heterogenic group. The etiology of the delayed progression of disease can be viral polymorphisms that impact replication and virulence, host genetic factors and immune factors.[24] Definitions of LTNP are varied in children; they can be defined as no progression of disease in the first ten years of life or CD4 percentages at or above 25 percent at 10 years.[25] It has also been defined as median survival of 12 to 13 years compared to the usual 6 years.[26] Depending on the definition, 3 to 25 percent of all children can be considered slow progressors.[26, 27] Although these children may have had few significant illnesses prior to presentation, they often present with AIDS defining events and subsequently have rapid progression of disease if they remain untreated. There is little data on whether these late presenters respond differently to antiretroviral therapy. It is important to keep HIV infection in the differential during the adolescent years since both late perinatal disease and early behavioral acquired transmissions can occur.

Survival to Adulthood

There is emerging data about perinatally acquired HIV disease beyond childhood. In US and Europe, the broad uptake of early HAART therapy has changed the epidemiology of disease.[28-30] Hospitalization rates have dramatically declined. Mortality rates have declined 90 percent as has rates of opportunistic infections.[28, 31] Despite enormous progress, the mortality rate in the US cohort continues to be 0.6 to 0.8 per 100,000 populations which is thirty times higher than rates in uninfected children. Multiorgan failure due to end stage AIDS was the most common cause of death. Many of these children were from earlier birth cohorts who entered care late. Initiation of antiretrovirals was associated with halving the risk of death in one study.[32] The mean age of most US and European pediatric cohorts is now above 15 years, and many youth are now transitioning into adult care.

Related to the long term survival of perinatally infected children are reports of pregnancy in young women with perinatal disease.[33] A prospective study from Manipur, India describes the pregnancy outcome of thirty young women with perinatal HIV. The mean age was 18 years and mean CD4 was 200. There were 4 elective abortions and 26 live births with only one premature delivery. Maternal and child outcomes were good, although complete data on perinatal transmission was not available. In a US study, there was a high rate of premature rupture of membranes and delivery but outcomes were still good. One out of ten infants studied acquired HIV infection.[34] Most studies have not shown a substantially different risk of mother-to- child transmission in this population but the numbers are very limited. The long term side consequences of pregnancy to the mothers and of exposure to their infants require further study.

In summary, the last twenty years of HIV care has demonstrated that we have the opportunity not only to eliminate maternal-to-child transmission of HIV but to alter the prognosis of children who are infected. The use of early antiretroviral therapy and supportive treatments will continue to extend survival. As these trends continue, it is imperative to monitor for long term side effects and treatment related metabolic consequences to assure optimal survival and quality of life.

Case Studies

Case 1

A 4-month-old female infant is born to a 20 years old G_1P_0 female via spontaneous vaginal delivery at 38 weeks gestation. Her mother received limited prenatal care in the third trimester and no HIV testing. She was not ill during pregnancy. Mother has been married for 3 years, Father is 35 years old and works in the city often travelling for 4 to 6 months at a time. He has also been healthy. Birth was uncomplicated; the birth weight was 2.8 kg.

The infant presents with respiratory distress, tachypnea and oxygen requirement. Now at 4 months of age, the weight is 3.5 kg. The exam reveals a small infant with mild respiratory distress. There is oral candidiasis, HSM, mild lymphadenopathy, increased tone, and a high pitched cry. The CXR shows diffuse interstitial infiltrates bilaterally. The infant is empirically started on trimethoprim sulfamethoxazole, and antituberculous therapy and steroids. The induced sputum for AFB is negative and a broncheolar lavage is not performed. An HIV antibody test is positive as is an HIV DNA PCR. Blood culture is negative. The infant improves with above medications and after 2 weeks the CD4 count is determined to be 300 and 10 percent.

The child described in Case 1 is a classic example of a rapid progressor who untreated, has a poor prognosis. In addition to supportive care and treatment for PCP, the key step is to initiate antiretroviral therapy. Even with HAART, she has an uncertain future. In multiple studies, children who start antiretrovirals while asymptomatic are much more likely to survive after five years compared to children with CDC Category C disease who start treatment.[13]

Case 2

A four-year-old male presents with a two month history of chronic cough, poor appetite, intermittent fevers and several kilo weight loss. His history is positive for chronic suppurative otitis media and recurrent respiratory infections often associated with wheezing. Height and weight z scores are -1.5 SD from average. CXR shows a reticulo-nodular pattern without significant hilar adenopathy. HIV antibody test is positive and confirmed; CD4 count is 750 and 25 percent

and viral load is 10,000 copies per ml. Extensive workup for tuberculoisis is negative and abnormal CXR is diagnosed as lymphoid interstitial pneumonitis.

Case 2 illustrates the presenting features of HIV after infancy. The patient described in Case 2 has a relatively good prognosis based on clinical symptoms such as LIP as well as CD4 and viral load levels. Utilizing the risk calculator based on HIV Pediatric Prognostic Markers Collaborative Study (HPPMCS) with CD4 count and age, his risk of progressing in the next twelve months is 3.5 percent for development of AIDS and a 0.3 percent risk of death.[23]

CASE 3

This is an eleven-year-old female who was referred to her doctor due to easy bruising. For the last several months she had increased fatigue and multiple bruises on her arms and legs. Her past medical history is significant for recurrent ear and sinus infections. Her only hospitalization was for suppurative parotitis at 6 years of age. She lived with her grandmother since her mother had died of pneumonia when she was 5 years of age. There is no history of sexual abuse. On exam she is small for her age; weight for height is at third percentile as is her height. In addition to the bruises, she has multiple hyperpigmented areas on her extremities from previous rashes. She also has moderate axillary and cervical lymphadenopathy noted. CBC shows a total platelet count of 80,000 and total WBC of 2,500 with 70 percent neutrophils and 30 percent lymphocytes, hemoglobin was 9.0. Her HIV antibody and western blot was positive. Her CD4 count is 150 and 5 percent and viral load is 30,000 copies. She was initiated on cotrimoxazole prophylaxis. A bone marrow done for her thrombocytopenia was consistent with Immune thrombocytopenia due to HIV. She was initiated on antiretroviral therapy of stavudine, lamuvidine and nevirapine and after 2 months platelets were in the normal range.

Case 3 illustrates a late presentation of perinatally acquired HIV infection. As many as 5 to 10 percent of HIV infected children will present after the age of 10 years with symptoms of HIV acquired from birth. This child required prompt initiation of antiretroviral therapy to treat both the immunodeficiency and the immune associated thrombocytopenia. There is little data regarding differences in long term response to treatment in late presenters. HIV disease should remain in the differential diagnosis of the older child who presents with any number of end organ or protean manifestations. Like syphilis, HIV has become a great mimicker.

Key Messages

- There is a bimodal distribution of pediatric HIV infection. A variety of factors impact pathogenesis and prognosis: Genetics of host, viral characteristics, co-infections and nutritional milieu.
- Early symptomatic HIV is associated with rapid progression and high mortality. Laboratory markers have poor prognostic value, therefore, WHO recommends treatment of all infected infants.
- For older children, the CD4 count and RNA viral load are independent predictors of disease progression. The advent of potent antiretroviral therapy has resulted in marked virologic control and immune reconstitution, and each later birth cohort has improved survival.

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1.4

Pharmacotherapy of Pediatric HIV Infection

Viraj B Mehta, Jaideep A Gogtay

Pediatric HIV Infection–Increasing Trends

Estimates show that the number of children living with HIV globally continues to increase steadily (Fig. 1.4.1). In India, HIV infection in children continues to be a growing challenge, with an estimated 100,000 infected women giving birth to about 30,000 infected infants every year.[1]

It is estimated that more than 90 percent of children living with HIV acquired the virus during pregnancy, birth or breastfeeding—modes of HIV transmission that can be prevented.[2]

Pediatric infections represent about 14 percent of new HIV infections that occur globally, and there is therefore a critical need to provide ART for infected infants and children.[3]

Goals of Therapy

Currently, there is no cure for HIV infection and viral eradication is not possible at this time. However, viral suppression to undetectable levels can be achieved, with careful selection of initial and subsequent regimens.[4] This allows the immune system to reconstitute.[5] Maximum viral suppression is thus, associated with delayed HIV disease progression and improved survival.[4] As a result, HIV infected infants and children may now survive to adolescence and adulthood.[3]

Goals of antiretroviral therapy in children

1. Inhibition of HIV replication
2. Preservation or restoration of immune function
3. Reduction of HIV associated morbidity and mortality
4. Permit normal growth and development

Life Cycle of HIV

The life cycle of HIV is depicted in Figure 1.4.2. HIV is a human retrovirus which contains the enzyme reverse transcriptase. During acute HIV infection, the viral envelope glycoprotein gp120 binds to the CD4 receptor on the mature human helper T lymphocyte (CD4 cell). Subsequently, the viral envelope binds to 1 of 2 chemokine coreceptors, either CXCR4 (X4) or CCR5 (R5). A conformational change then ensues, resulting in the fusion of the viral envelope with the CD4 cell membrane. Next, the HIV viral RNA enters the cell cytoplasm. The viral reverse transcriptase then transcribes the single-stranded viral RNA into double stranded DNA. The viral enzyme integrase inserts the proviral DNA into the host genome via-a strand transfer reaction.

During subsequent activation of this infected CD4 cell, the integrated proviral DNA is translated into new viral proteins. Assembly of these viral products then occurs on the cell surface, followed by budding of immature viral particles. The viral enzyme protease aids in the production of final infectious virions by cleaving viral polyprotein precursors, and generating new viral proteins.

Active viral replication then occurs in the human host. Eventually it decreases over time to a steady state level. A progressive immunodeficiency is seen over time, which may culminate in the occurrence of opportunistic infections, malignancy and death.[4]

Drug therapy uses agents in combination that act at different phases of the virus life cycle (Fig. 1.4.2).

Overview of Antiretroviral Medications

There are 22 antiretroviral drugs approved by the US FDA that are currently in use for the treatment of HIV infected adults and adolescents. These drugs belong to five major classes:

1. Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs/NtRTIs)
2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
3. Protease inhibitors (PIs)

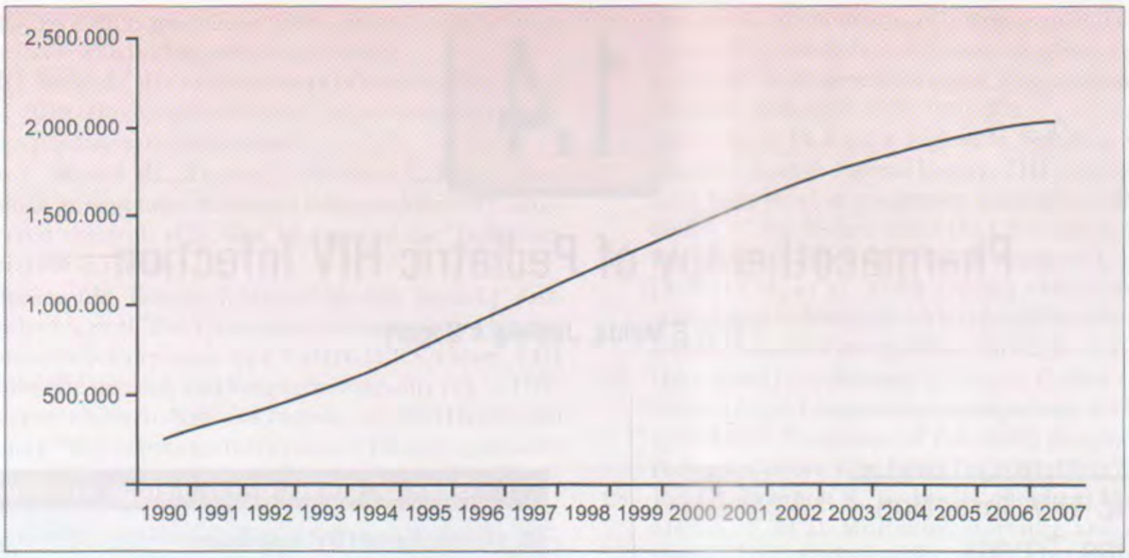


Fig. 1.4.1: Children living with HIV globally, 1990-2007[2]

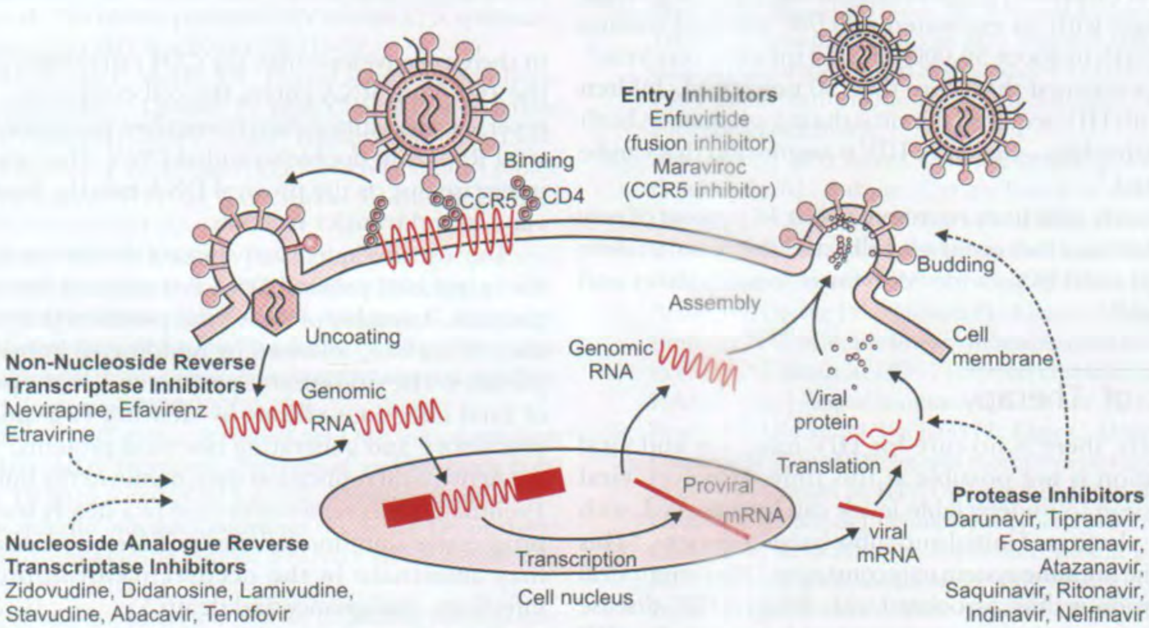


Fig. 1.4.2: Target sites of drugs for HIV
Adapted from Medicine, 37(7), Alasdair Breckenridge, Pharmacology of drugs for HIV, pg 375, 2009

4. Entry inhibitors (including fusion inhibitors and CCR5 receptor antagonists)
5. Integrase inhibitors

Although many of the medications used for treating children are the same as those used in adults, issues unique to pediatric HIV infection include differences in mode of viral acquisition, immaturity of the immune system, and considerations of growth and development, especially during puberty as well as differences in pharmacokinetics, availability of suitable drug formulations, and importance of family issues with regard to drug giving and adherence.[4]

Combination antiretroviral therapy for the treatment of HIV infection in children was introduced about 13 years ago. At that time, most research and knowledge of these drugs was based on experience from treating adults. However, rapid developments have taken place since then. Approximately 17 different antiretroviral drugs have now been developed to treat HIV infection in children (Table 1.4.1).[5]

Treatment decisions must include consideration of the child's age, treatment readiness, psychosocial milieu, past treatment history, as well as available drug formulations

Table 1.4.1: Classes of antiretroviral drugs**

Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTIs/NtRTIs)	*Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)*	*Protease Inhibitors (PIs)*	*Entry Inhibitors*	*Integrase Inhibitors*
NRTIs	Nevirapine* (NVP)	Atazanavir* (ATV)	***Fusion inhibitor***	Raltegravir
Abacavir* (ABC)	Efavirenz* (EFV)	Darunavir* (DRV)	Enfuvirtide* (T20)	
Didanosine* (ddl)	Etravirine (ETV)	Fosamprenavir* (fAMP)	***Entry blocker***	
Emtricitabine* (FTC)		Indinavir (IDV)	Maraviroc	
Lamivudine* (3TC)		Lopinavir/ritonavir* (LPV)		
Stavudine* (d4T)		Nelfinavir* (NLF)		
Zidovudine* (AZT)		Ritonavir* (RTV)		
NtRTI		Saquinavir (SQV)		
Tenofovir disoproxil fumarate (TDF)		Tipranavir* (TPR)		

*Approved for use in children

**Three drugs—zalcitabine, amprenavir and delavirdine—are no longer manufactured, and do not appear in this table.

and treatment schedule. Possible drug teratogenicity must be considered in the treatment of adolescents who may be sexually active.[4]

The following section gives an overview of the currently available antiretrovirals. More detailed information is available in "Supplement I: Pediatric Antiretroviral Drug Information" (February 23, 2009).[6]

Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTIs/NtRTIs)[6-11]

Mode of Action

The enzyme reverse transcriptase plays a crucial role, in that it catalyzes the transcription of single-stranded viral RNA to double-stranded DNA that is subsequently incorporated into the nucleus of the invaded CD4 cell. NRTIs are prodrugs which are activated intracellularly by phosphorylation, forming triphosphates that mimic naturally occurring nucleotides. Once incorporated in place of the natural nucleoside, they cause DNA chain termination and inhibition of reverse transcriptase.

Tenofovir has a mode of action similar to nucleoside reverse transcriptase inhibitors, but is structurally a nucleotide, and as such does not require the initial phosphorylation reaction, which is often rate-limiting for nucleoside analogues. Tenofovir diphosphate is the active form, which competes with the natural nucleoside and causes DNA chain termination.

Resistance

Mutations to reverse transcriptase that confer resistance to zidovudine occur at codon 70, to lamivudine at codon 184, to didanosine and abacavir at codons 74 and 184, and to stavudine at codon 75. The tenofovir-associated mutation occurs at codon 65.

There is a variable amount of cross resistance among the NRTIs. Thymidine Analog Mutations (TAMs) reduce susceptibility to all NRTIs. The most frequent TAMs with the greatest impact on NRTI susceptibility are 41L, 210W and 215Y.

Antagonism has been reported among specific reverse transcriptase mutations. A relevant example is the antagonism among various thymidine analog NRTIs, TAM and the emergence of the tenofovir-associated K65R mutation. TAMs selected by zidovudine or stavudine counteract the selection of the K65R mutation. Thymidine analog NRTIs such as zidovudine may protect against the emergence of the K65R mutation when combined with tenofovir. This mechanism can be favorably harnessed in clinical practice by using a combination of both these agents.

The M184V mutation that causes resistance to lamivudine and emtricitabine increases susceptibility to zidovudine and tenofovir and reduces emergence of TAMs.[12,13]

Clinical Pharmacology

The bioavailability of the NRTIs varies from 30-40 percent for didanosine, 60 percent for zidovudine and 80 percent for abacavir. Except for lamivudine (5-7 hours) and emtricitabine (about 10 hours), their plasma half-life is short (1-2 hours). For all these molecules, the intracellular half-life of the active triphosphate metabolite is much longer (usually 4-6 hours). In terms of elimination pathways, zidovudine forms a glucuronide in the liver, whereas didanosine, stavudine and lamivudine are predominantly excreted unchanged by the kidney (50%, 75%, 40% and 70%, respectively). Abacavir is the only NRTI that does not require dose adjustment for renal dysfunction.

Tenofovir has a bioavailability of 25 percent, and a plasma half life of 17 hours. It is largely eliminated by renal excretion. Tenofovir is available as tenofovir disoproxil fumarate, which undergoes esterase hydrolysis in the gastrointestinal tract to yield tenofovir.

Adverse Reactions

All NRTIs carry a black box warning for lactic acidosis. Stavudine, zidovudine and didanosine are thought to carry a higher risk due to increased mitochondrial toxicity. Zidovudine has potential to cause bone marrow suppression and macrocytosis, and stavudine and didanosine may cause peripheral neuropathy and pancreatitis. Abacavir hypersensitivity reactions are characterized by fever and rash and may be fatal. Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. Prior to initiating therapy with abacavir, screening for the HLA-B*5701 allele has been shown to decrease this risk. Some adult data suggest an association between abacavir use and increased risk of myocardial infarction. Emtricitabine may cause liver function abnormalities. Nausea and loss of appetite are associated with all NRTIs. Tenofovir can cause liver damage, hypophosphatemia and renal failure with a Fanconi-like syndrome. Regular monitoring of renal function and serum phosphate levels is advised. NRTIs, particularly stavudine and zidovudine, can cause lipoatrophy and increased lipid levels.

Drug Interactions

Both the thymidine analog stavudine and zidovudine compete for the same intracellular activation pathway. Lamivudine and emtricitabine (both cytosine analogs) should not be combined since they are essentially identical in action and resistance profile. The didanosine-stavudine combination carries an increased risk for peripheral neuropathy and pancreatitis. The combination of the adenosine analogs didanosine and tenofovir causes a paradoxical fall in CD4 counts and risk of treatment failure and is not recommended.

Pediatric Experience

All the approved NRTIs for pediatric use have been evaluated extensively. Whereas some earlier studies dealt with monotherapy or dual therapy, later studies have focused on a variety of triple drug regimens. The 3 NRTI combination of abacavir/zidovudine/lamivudine has also been evaluated, although this combination should be used only in special circumstances. Didanosine has been evaluated in a range of doses, administered both once daily and twice daily. Lamivudine is an important component of fixed-dose combination tablets with d4T and nevirapine that have facilitated scaling-up of antiretroviral therapy in resource-limited settings. Lamivudine and zidovudine have been given to infants during the first 6 weeks of life; both are available in a liquid formulation.

Tenofovir is currently under investigation for pediatric use. A 75 mg tablet formulation has been studied in children aged 6-18 years, and a liquid formulation has been evaluated in younger children (2-8 years). There are conflicting data on the effect on bone in treatment-experienced children; no bone mineral density studies have been performed in treatment-naïve children who initiate therapy with tenofovir. Recently, tenofovir has been given an orphan drug status in Australia and is approved for use in children aged between two and 17 years of age.[14]

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)[6-10]

Mode of Action

NNRTIs also inhibit reverse transcriptase, but by a different mechanism from that of the NRTIs. NNRTIs directly bind to reverse transcriptase and inhibit it. They are combined with NRTIs, because of a synergistic or additive action.

Resistance

Efavirenz and nevirapine have a low resistance barrier. Cross-resistance exists between these two drugs. The new NNRTI etravirine has a higher barrier to the development of resistance, and may retain activity against virus resistant to the earlier NNRTIs, depending on the presence of specific mutations. The K103N mutation, which is often seen in patients experiencing virologic failure during nevirapine or efavirenz treatment, is not associated with etravirine resistance.

However, there is no cross-resistance between NRTIs and NNRTIs because of the different mechanisms of binding to and inhibition of reverse transcriptase, resulting in non-overlapping mutations associated with resistance to either class. Viral isolates with reduced susceptibility to a NRTI may possess hypersusceptibility to NNRTIs.[12]

Clinical Pharmacology

Nevirapine is about 93 percent bioavailable; it readily crosses the placenta and is also found in breast milk. The oral bioavailability of efavirenz is good, though lower bioavailability has been reported with the liquid formulation. Food intake increases C_{max} and AUC of efavirenz compared with fasting conditions. Efavirenz readily crosses the blood-brain barrier, with cerebrospinal fluid concentrations ranging from 0.26 to 1.19 percent of that in blood plasma. The plasma half lives of nevirapine, efavirenz and etravirine range from 30-40 hours. NNRTIs

are metabolized through the CYP3A4 isoform of cytochrome P450 in the liver, and are thereby involved in several drug interactions.

When starting nevirapine, patients are instructed to take nevirapine once daily for the first 14 days and subsequently increase to twice daily. This is because nevirapine induces its own metabolism, and can cause severe hypersensitivity reactions.

Adverse Reactions

NNRTIs can cause hypersensitivity reactions, with nevirapine having the highest potential. The reactions may vary from simple rashes to Stevens-Johnson syndrome and liver dysfunction. Patients with higher CD4 counts are at increased risk for hepatotoxicity from nevirapine. Efavirenz has a unique set of central nervous system side effects that includes drowsiness and vivid dreams. Gastrointestinal side effects and rash are seen with etravirine.

Drug Interactions

Since the NNRTIs are metabolized by CYP3A4, both inducers and inhibitors of CYP3A4 lead to alterations in NNRTI plasma levels.

Pediatric Experience

Both nevirapine and efavirenz have been studied in combination with NRTIs and a PI. The bioavailability of efavirenz liquid has been reported to be 20 percent lower than that of the capsules, hence trials using the liquid formulation have used a higher dose. Antiviral effects have been reported to be similar in children receiving either formulation. The impact of single-dose nevirapine exposure (during prophylaxis to prevent vertical transmission of HIV) on the efficacy of subsequent nevirapine-based therapy in infected children is currently under study. Data on the use of efavirenz in children below 3 years of age are sparse, hence nevirapine is preferred in this age group.

Protease Inhibitors (PIs)[6-10]

Mode of Action

Protease inhibitors inhibit the enzyme protease, which cleaves the large viral polyprotein strands into individual pieces required for making new functional virions. Thus, formation of mature virion particles capable of infecting new CD4 cells is prevented.

Resistance

The genetic barrier to resistance (i.e. the number of mutations required for resistance to develop combined with difficulty in their selection) is generally greater for ritonavir-boosted PI-containing regimens than it is for unboosted PI-containing regimens. Resistance to ritonavir-boosted PIs requires multiple mutations that vary among PIs, and the degree of resistance depends on the number, as well as the type, of mutations present. The large number of mutations required for resistance makes the selection of resistance to boosted PI regimens uncommon.

Newer PIs such as darunavir and tipranavir, have improved virologic activity in patients harboring PI-resistant HIV-1[12]

Clinical Pharmacology

The current standard of care is to administer protease inhibitors with a low "boosting" dose of ritonavir. Ritonavir is a strong inhibitor of CYP3A4, which is involved in metabolizing most PIs. Thus, plasma levels of PIs are raised by inhibiting metabolism. The only protease inhibitor that is not boosted with ritonavir is nelfinavir, since it is not metabolized primarily by CYP3A4. Lopinavir is the only PI that is currently available as a coformulation with ritonavir.

The plasma half-lives of indinavir, nelfinavir and ritonavir are relatively short (2-4 hours) and those of atazanavir, tipranavir and fosamprenavir are 7-8 hours. Darunavir has a half-life of 15 hours. All PIs except indinavir are eliminated by hepatic metabolism involving cytochrome P450 CYP3A4. PIs may have altered kinetics in pregnancy.

Generally, PIs are inhibitors of CYP3A4. The exception is tipranavir, which is an inducer and therefore must be given with a higher dose of ritonavir for boosting.

Several protease inhibitors, e.g. saquinavir have under gone extensive reformulation in an attempt to improve bioavailability, decrease pill burden and eliminate the requirement for refrigeration.

In patients with renal failure, only atazanavir, darunavir, fosamprenavir and tipranavir may be used at their usual dosages, unlike other PIs.

Adverse Reactions

PIs have been associated with long-term metabolic effects including increased triglycerides, increased blood glucose and fat redistribution. Atazanavir is thought to have the least effect on lipids. As a class, PIs may increase the risk of bleeding in patients with hemophilia.

Gastrointestinal side effects occur with all PIs. Tipranavir carries a black box warning for intracranial hemorrhage. Indirect hyperbilirubinemia seen with atazanavir is usually subclinical; scleral icterus may be present. Nephrolithiasis has also been reported with atazanavir. PIs such as fosamprenavir, darunavir and tipranavir contain a sulfa moiety and could provoke a

reaction in an individual with sulfonamide allergy; this cross-sensitivity is rarely seen clinically. Indinavir can cause hyperbilirubinemia and nephrolithiasis.

Drug Interactions

Due to their metabolism by CYP3A4, there are several drug interactions. The use of some drugs (ergot alkaloids, simvastatin, lovastatin, midazolam, triazolam, inducing anticonvulsants, rifampin, St John's wort and fluticasone) is contraindicated with PIs as a class. Further, individual PIs may have additional severe drug interactions. Some other interactions may require dose modifications. Atazanavir interacts with most acid reducing agents.

Pediatric Experience

Atazanavir has been studied in children, both boosted and unboosted. In addition to capsules, a powder formulation is under study. Darunavir has only been evaluated in treatment-experienced children, and is currently not recommended for treating antiretroviral-naive children. Fosamprenavir has been evaluated in both antiretroviral-naïve and experienced children. There is insufficient data from clinical trials regarding once-daily dosing of boosted fosamprenavir, hence it is not recommended for children.

Lopinavir/ritonavir has been evaluated in combination with NRTIs and NNRTIs in naïve and experienced patients. A sprinkle formulation is currently under development for pediatrics.[15] Although nelfinavir has been extensively studied in pediatrics, it cannot be boosted with ritonavir and consequently is no longer preferred. Although ritonavir has been well studied, its use as a sole PI for initial therapy is not recommended. Tipranavir has been evaluated mainly in treatment-experienced patients. Tipranavir oral solution contains 116 IU per ml of vitamin E, and patients receiving this formulation should not take any supplemental vitamin E greater than a standard multivitamin.

Indinavir has been studied as monotherapy and combination therapy in mostly small uncontrolled trials, and is not approved in pediatrics. Although both saquinavir/ritonavir and saquinavir/lopinavir/ritonavir appear to be promising regimens for children, the appropriate dosing is not known.

Entry Inhibitors[6-10]

Mode of Action

These drugs act by interfering with the binding, fusion and entry of the virus into human cells. Enfuvirtide (T20) binds to gp41 whereas maraviroc binds to the CCR5 coreceptor found on the surface of some CD4 cells.

Resistance

HIV isolates with reduced susceptibility to T20 have been selected *in vitro* although primary resistance to T20 in patients without prior T20 treatment is very rare. The entry of CXCR4-tropic and dual-tropic HIV into CD4 cells is not inhibited by maraviroc, and drug resistant maraviroc variants can be selected during treatment due to a coreceptor switch from CCR5-tropic virus to CXCR4-using virus.

Clinical Pharmacology

Enfuvirtide is supplied as a powder for injection and administered as a subcutaneous injection twice daily, and is usually used in extensively treatment-experienced patients. It is approximately 92 percent protein bound, predominantly to albumin. It undergoes catabolism to its constituent amino acids and does not affect the metabolism of drugs metabolized by liver CYP450 enzymes.

Some HIV viruses can use either the CCR5 or CXCR4 coreceptor, whereas some use one or the other. Consequently, before using maraviroc, a tropism assay is required to assess a particular patient's virus tropism.

Adverse Reactions

Adverse effects of enfuvirtide include injection site reactions and hypersensitivity reactions. The high incidence of local injection site reactions (98%) limits the use of fusion inhibitors in pediatric patients. Hepatotoxicity has been reported with maraviroc.

Drug Interactions

Maraviroc is associated with many drug interactions, with dosage adjustments required depending on whether the concomitantly administered drugs are CYP3A inducers or inhibitors.

Pediatric Experience

Enfuvirtide has been studied in treatment-experienced patients, and maraviroc has not been studied in children under 16 years of age.

Integrase Inhibitor[6-10]

Raltegravir targets integrase, the enzyme responsible for integrating the viral genes into human chromosomes. Resistance is associated with integrase mutations at either Q148 or N155.

Raltegravir is metabolized by glucuronidation and has a half life of 9 hours. These include gastrointestinal upsets,

dizziness and asthenia. Creatine kinase elevations have been observed.

Raltegravir should be used with caution when coadministered with strong inducers of UGT1A1, including rifampicin. Raltegravir has not been studied in children under 16 years of age.

Pharmacological Considerations in Children

There are a number of pharmacological considerations to take into account before prescribing antiretrovirals in children. These are as follows:

1. As a first general principle, children are not just small adults but are clearly pharmacokinetically distinct. Physiological changes occurring with age dictate drug absorption, distribution, metabolism and excretion in children, which can differ significantly from the same processes in adults. In pediatric patients, the absorption of drugs may be potentially influenced by several factors such as gastric acid secretion, gastric emptying time, intestinal transit time, and gastrointestinal motility. The age related differences in drug distribution and elimination in children are attributed to the varying rates at which the organs involved in drug elimination develop, the different body composition between adults and children, and the potential endocrinologic effects related to puberty. Successful antiretroviral therapy in children thus depends on our ability to adjust antiretroviral dosing according to these changes. Further, there is limited data on the impact of malnutrition on antiretroviral pharmacokinetics.[16,17]
2. Secondly, pediatric dosing is based on age, weight, and/or body surface area. Typically, dosing recommendations stratify children by age, and doses are given in either a mg/kg or mg/m^2 basis. However, age stratification cannot accommodate children of the same age who have quite different weights and organ functions. The choice of mg/kg or mg/m^2 may have clinical implications because an approach for young children based on body surface area will give a much higher dose than will one based on body weight. A more individualized approach to dosing is possible with the use of therapeutic drug monitoring.[16]
3. Development of pharmaceutically elegant pediatric formulations is another critical consideration. Liquid formulations are essential for the youngest children who cannot swallow solid dosage forms but can be broadly useful because they allow for individualized dosing as children grow. They are also simpler to mix with food or liquid. However, the need for oral syringes, refrigeration for some drugs and special dispensing bottles impedes adherence, making these formulations less desirable. The palatability of liquid formulations for the nucleosides has been quite acceptable. However, those for the protease inhibitors has been modest at best.[16,17]

Antiretroviral formulations must not only be palatable but easy to administer, since adherence in children is dependent on the dedication of caregivers (in many cases elderly grandparents or older siblings).[18] Chewable or orally disintegrating tablets are an attractive alternative.

A number of fixed drug combinations (FDCs) have proven convenient for ART administration in adults. Their main advantage is ease of use with lower pill burdens.[8] Fixed-dose combination products specific for pediatric dosing are vital to medication adherence in this patient population.[17] In order to simplify dosing guidance in busy clinics, the World Health Organisation (WHO) has developed weight band dosing charts based on body surface area.[19] This chart's usefulness is dependent on the availability of pediatric FDC formulations which better approximate optimal antiretroviral doses in children.[16] One such FDC product—Triomune Baby/Junior (stavudine 6/12 mg + lamivudine 30/60 mg + nevirapine 50/100 mg dispersible tablets manufactured by Cipla) – is already being widely used in various developing countries. A 2-NRTI combination—Lamivir-S Baby/Junior (stavudine 6/12 mg + lamivudine 30/60 mg; also manufactured by Cipla) – is also available to facilitate the initial 14-day lead-in dosing of nevirapine, i.e during the first two weeks. Triomune is administered in the morning, and Lamivir-S in the evening. Several other two- and three-drug combinations are under development for use in pediatrics.

Table 1.4.2 and Table 1.4.3 lists the various pediatric formulations available, with dosing recommendations.

Drug Interactions[20]

Treatment of HIV infection requires long-term administration of multiple antiretroviral drugs, and often other medications for opportunistic infections, concomitant illnesses, or management of side effects. This unavoidable polypharmacy means that drug-drug interactions are inevitable.

Drug-drug interactions are either pharmacokinetic (PK) or pharmacodynamic (PD). PK interactions result from alterations in drug absorption, distribution, metabolism or elimination and lead to altered concentrations in the body. PD interactions are the result of synergistic, additive, or antagonistic drug effects or toxicities.

The field of antiretroviral drug-drug interactions is rapidly changing, and clinicians are advised to always consult the most up-to-date references. Online interactive databases (Table 1.4.4) are an excellent source of

Table 1.4.2: Available formulations and dosing of antiretrovirals in children[9,10]

<table>
<tr><th>Drug Age
[Pediatric Approval by US FDA]</th><th>Formulation</th><th>Dose</th></tr>
<tr><td>Zidovudine (AZT) 0-18 years [1990]</td><td>• Oral solution 10 mg/ml
• Tablet 300 mg
• Capsule 100 mg
• Concentrate for injection/for intravenous infusion: 10 mg/ml</td><td>Dose for premature infants for prevention of transmission or treatment (standard neonatal dose may be excessive in premature infants):
1.5 mg per kg of body weight (intravenous) or 2 mg per kg of body weight (oral) every 12 hours, increased to every 8 hours at 2 weeks of age (neonates ≥30 weeks gestational age) or at 4 weeks (neonates <30 weeks gestational age).
Neonatal/Infant dose (age <6 weeks) for prevention of transmission or treatment:
Oral: 2 mg per kg of body weight every 6 hours.
Intravenous: 1.5 mg per kg of body weight every 6 hours.
Pediatric dose (age 4 weeks to <18 years):
Oral dosing:
Pediatric Patients (age 4 weeks of age and older and weighing ≥4 kg)
<table>
<tr><th>Body weight</th><th>Twice daily dosing</th><th>Thrice daily dosing</th></tr>
<tr><td>4 kg to <9 kg</td><td>12 mg/kg</td><td>8 mg/kg</td></tr>
<tr><td>≥9 kg to <30 kg</td><td>9 mg/kg</td><td>6 mg/kg</td></tr>
<tr><td>≥30 kg</td><td>300 mg</td><td>200 mg</td></tr>
</table>
Alternatively, 240 mg per m^2 of body surface area every 12 hours or 160 mg per m^2 every 8 hours.
Intravenous dosing:
Intermittent infusion: 120 mg per m^2 of body surface area every 6 hours.
Continuous infusion: 20 mg per m^2 of body surface area per hour.
Adolescent (age ≥ 18 years)/Adult dose: 200 mg 3 times a day or 300 mg twice daily.</td></tr>
<tr><td>Didanosine (ddI) 2 weeks-18 years [1991]</td><td>• Powder for oral solution (when reconstituted as solution containing antacid): 10 mg/mL
• Delayed release capsule 125 mg, 200 mg, 250 mg, and 400 mg</td><td>Neonatal/Infant dose (infants aged 2 weeks to 8 months)
Usual dose of oral solution:
100 mg per m^2 of body surface area every 12 hours.
Pediatric (age >8 months)
Usual dose of oral solution:
100 mg per m^2 of body surface area every 12 hours; clinical studies have used a pediatric dose range of 90-150 mg per m^2 of body surface area every 12 hours.
In treatment—naïve children aged 3-21 years, 240 mg per m^2 of body surface area once daily (maximum 400 mg) has been used with good viral suppression (PACTG 1021).
Pediatric Patients (ages 6-18 years and weighing >20 kg and able to swallow capsules)</td></tr>
</table>

<table>
<tr><th>Drug Age
[Pediatric Approval by US FDA]</th><th>Formulation</th><th>Dose</th></tr>
<tr><td></td><td></td><td>Delayed Release Capsules
<table><tr><th>Body weight</th><th>Dose</th></tr><tr><td>20 kg to less than 25 kg</td><td>200 mg od</td></tr><tr><td>25 kg to less than 60 kg</td><td>250 mg od</td></tr><tr><td>At least 60 kg</td><td>400 mg od</td></tr></table>
Adolescent/Adult dose:
Oral solution:
Body weight ≥60 kg: 200 mg twice-daily.
Body weight <60 kg: 125 mg twice-daily.
The total daily dose (400 mg or 250 mg, depending on weight) may be administered once daily in adolescents/adults to improve complaince; however, the preferred dosing frequency is twice daily because there is more evidence to support the effectiveness of this regimen.
Delayed release capsule formulation:
Body weight ≥60 kg: 400 mg once daily.
Body weight <60 kg: 250 mg once daily.</td></tr>
<tr><td>Lamivudine (3TC) 0-18 years [1995]</td><td>• Oral solution 10 mg/ml
• Tablet 150 mg (scored) and 300 mg</td><td>Neonatal/Infant dose (infants aged <30 days): 2 mg per kg of body weight twice-daily.
Pediatric dose: 4 mg per kg of body weight (maximum dose, 150 mg) twice-daily.
150 mg Scored Tablets (≥14 kg)
<table><tr><th>Weight (kg)</th><th>AM dose</th><th>PM dose</th></tr><tr><td>14-21</td><td>½ tablet (75 mg)</td><td>½ tablet (75 mg)</td></tr><tr><td>>21-<30</td><td>½ tablet (75 mg)</td><td>1 tablet (150 mg)</td></tr><tr><td>≥30</td><td>1 tablet (150 mg)</td><td>1 tablet (150 mg)</td></tr></table>
Adolescent (age ≥16 years)/Adult dose:
Body weight ≥50 kg: 150 mg twice daily or 300 mg once daily. Body weight <50 kg: 4 mg per kg of body weight (maximum dose, 150 mg) twice daily.</td></tr>
<tr><td>Stavudine (d4T) 0-18 years [1996]</td><td>• Oral solution 1 mg/ml
• Capsule 15 mg, 20 mg, 30 mg, and 40 mg</td><td>Neonatal/Infant dose (age birth to 13 days):
0.5 mg per kg of body weight every 12 hours.
Pediatric dose (age 14 days up to weight of 30 kg): 1 mg per kg of body weight every 12 hours.
Adolescent (weight ≥30 kg)/Adult dose:
Body weight 30-<60 kg: 30 mg twice daily.
Body weight ≥60 kg: 40 mg twice daily (WHO recommends the use of 30 mg bd)</td></tr>
</table>

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Drug Age [Pediatric Approval by US FDA]	*Formulation*	*Dose*
Abacavir (ABC) *3 months-18 years* [1996]	• Oral solution 20 mg/ml • Tablet 300 mg	*Neonatal/Infant dose:* Not approved for use in infants aged <3 months. *Pediatric (age ≥3 months) dose:* 8 mg per kg of body weight (maximum dose 300 mg) twice daily. *Adolescent dose:* Data from clinical trials support the use of the adult dose of 300 mg twice daily for adolescents. *Adult dose (>16 years):* 300 mg twice daily or 600 mg once daily.
Emtricitabine (FTC) *3 months-16 years* [2003]	• Oral solution 10 mg/ml • Capsule 200 mg	*Neonatal/Infant dose:* Not approved for use in neonates/infants <3 months of age. *Pediatric (age 3 months through 17 years) dose:* Oral solution: 6 mg per kg of body weight (maximum dose 240 mg) once daily. Capsules (for patients weighing >33 kg): 200 mg once daily. *Adolescent (age ≥18 years)/Adult dose:* Capsules: 200 mg once daily. Oral solution: 240 mg (24 ml) administered once daily.
Tenofovir* (TDF) ≥ *12 years* [2010]	• Tablet 300 mg	*Adolescents (≥12 years and ≥35 kg):* 300 mg once daily
Efavirenz (EFV) 3-18 years [1998]	• Tablets 50 mg and 200 mg • Capsules 50 mg and 200 mg • liquid formulation 30 mg/ml**	*Neonatal/Infant dose:* Not approved for use in neonates/infants. *Pediatric dose* There are currently no data available on the appropriate dosage for children <3 years of age. *For children ≥3 years of age and weight ≥10 kg):* Administer once daily: (see EFV dosing table below) * The dose in mg could be dispensed in any combination of capsule strengths; dose represents the maximum recommended EFV dose for each weight band. *Adolescent (weight ≥ 40 kg)/Adult dose:* 600 mg once daily.

Body weight		EFV dose (mg)*
Kg	Lbs	
10-<15	22-<33	200
15-<20	33-<44	250
20-<25	44-<55	300
25-< 32.5	55-<71.5	350
32.5<40	71.5-<88	400
≥ 40	≥ 88	600

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<table>
<tr><th>Drug Age
[Pediatric Approval by US FDA]</th><th>Formulation</th><th>Dose</th></tr>
<tr><td>Nevirapine (NVP) 0-18 years [1998]</td><td>• Oral Suspension 10 mg/ml
• Tablet 200 mg</td><td>Neonatal/Infant dose (age <14 days):
Dose used for NVP prophylaxis of mother to child HIV transmission was 2 mg per kg body weight given as a single dose between birth and age 3 days. Treatment dose not defined for infants <14 days of age.
Pediatric dose (15 days and older): Initiate therapy with 150 mg per m^2 of body surface area (maximum dose, 200 mg) administered once daily for the first 14 days. If no rash or untoward effects, increase to full dose, 150 mg per m^2 of body surface area administered twice daily (maximum dose, 200 mg twice daily); younger children (e.g. age <8 years) may require a higher dosage (i.e. 200 mg per m^2 of body surface area twice daily). The total daily dose should not exceed 400 mg.
Adolescent/Adult dose: 200 mg twice daily. Note: Initiate therapy with 200 mg given once daily for the first 14 days. Increase to 200 mg administered twice daily if there is no rash or other untoward effects.</td></tr>
<tr><td>Nelfinavir (NLF) 2-18 years [1997]</td><td>• Powder for oral suspension 50 mg per one level gram scoop full (200 mg per one level teaspoon)
• Tablets 250 mg, 625 mg</td><td>Neonatal/Infant dose: Not approved for use in neonates/infants.
Pediatric dose (age 2-13 years): 45-55 mg per kg of body weight twice daily or 25-35 mg/kg 3 times daily, with a meal.
Dosing for children ≥ 2 yrs using 250 mg tablets.
<table>
<tr><th rowspan="2">Body weight (kg)</th><th colspan="2">Number of tablets (kg)</th></tr>
<tr><th>Twice daily
45-55 mg/kg</th><th>Thrice daily
25-35 mg/kg</th></tr>
<tr><td>10-12</td><td>2</td><td>1</td></tr>
<tr><td>13-18</td><td>3</td><td>2</td></tr>
<tr><td>19-20</td><td>4</td><td>2</td></tr>
<tr><td>>21</td><td>4-5*</td><td>3**</td></tr>
</table>
*for bid dosing, max dose per day is 5 tabs bid
**for tid dosing, max dose per day is 3 tablets tid
For children unable to take tablets, nelfinavir oral powder may be administered (4 level scoops equals 1 level teaspoon)</td></tr>
</table>

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<table>
<tr><th>Drug Age
[Pediatric Approval by US FDA]</th><th>Formulation</th><th>Dose</th></tr>
<tr><td></td><td></td><td>Dosing for children ≥ 2 yrs, using powder
<table>
<tr><th rowspan="2">Body weight (kg)</th><th colspan="2">Twice daily 45-55 mg/kg</th><th colspan="2">Thrice daily 25-35 mg/kg</th></tr>
<tr><th>Scoops of powder</th><th>Teaspoons of powder</th><th>Scoops of powder</th><th>Teaspoons of powder</th></tr>
<tr><td>9.0 to <10.5</td><td>10</td><td>2.5</td><td>6</td><td>1.5</td></tr>
<tr><td>10.5 to <12</td><td>11</td><td>2.75</td><td>7</td><td>1.75</td></tr>
<tr><td>12 to < 14</td><td>13</td><td>3.25</td><td>8</td><td>2</td></tr>
<tr><td>14 to <16</td><td>15</td><td>3.75</td><td>9</td><td>2.25</td></tr>
<tr><td>16 to <18</td><td>NR</td><td>NR</td><td>10</td><td>2.5</td></tr>
<tr><td>18 to <23</td><td>NR</td><td>NR</td><td>12</td><td>3</td></tr>
<tr><td>≥23</td><td>NR</td><td>NR</td><td>15</td><td>3.75</td></tr>
</table>
NR = not recommended; use 250 mg tabletAdolescent/Adult dose: 1,250 mg (five 250 mg tablets or two 625 mg tablets) twice daily or 750 mg (three 250 mg tablets) 3 times daily with a meal.</td></tr>
<tr><td>Ritonavir* (RTV) 1 month-18 years [1997]</td><td>• Oral solution (note: contains 43% alcohol by volume): 80 mg/ml
• Tablet 100 mg</td><td>Ritonavir as a pharmacokinetic enhancer: The major use of RTV is as a pharmacokinetic enhancer of other PIs. The dose of ritonavir recommended varies with the different protease inhibitors. See dosing information for specific PI.
Neonatal/Infant dose: Not approved for use in neonates/infants aged <1 month.
Pediatric (age >1 month): The full dose of 350-450 mg per m² of body surface area twice daily (maximum dose of 600 mg) is recommended in the unusual situation when RTV is prescribed as the sole PI. Dose escalation over several days is recommended to minimize gastrointestinal toxicity.
Adolescent/Adult dose: 600 mg twice daily. To minimize nausea/vomiting, initiate therapy starting at 300 mg twice daily and increase at 2 to 3 day intervals by 100 mg twice daily.</td></tr>
<tr><td>Lopinavir/ritonavir (LPV) 2 weeks-18 years [2000]</td><td>• Liquid (note: contains 42.4% alcohol by volume): 80 mg LPV/20 mg RTV per ml
• Tablet 200 mg LPV/50 mg RTV and pediatric tablets 100 mg LPV/25 mg RTV</td><td>Once daily dosing is not recommended.
Dose can be calculated based on weight or BSA.
Based on Weight:
Patient Weight (kg) × Prescribed lopinavir dose (mg/kg) = Administered lopinavir dose (mg)
Based on BSA:
Patient BSA (m²) × Prescribed lopinavir dose (mg/m²) = Administered lopinavir dose (mg)
If oral solution is used, the volume (ml) solution can be determined as:</td></tr>
</table>

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<table>
<tr><th>Drug Age
[Pediatric Approval by US FDA]</th><th>Formulation</th><th>Dose</th></tr>
<tr><td></td><td></td><td>
Volume of solution (ml) = Administered lopinavir dose (mg) ÷ 80 (mg/ml)

Neonatal/Infant dose (infants aged 14 days to 6 months): The recommended dose of the oral solution is 300 mg LPV per m² of body surface area/75 mg RTV per m² body surface area, or 16 mg LPV per kg body weight/4 mg RTV per kg body weight twice daily. It is recommended LPV/RTV not to be administered in combination with EFV, NVP, f-APV, or NFV in infants <6 months.

NOTE: Use of 300 mg LPV per m² of body surface area in infants age <6 months, particularly those age <6 weeks, is associated with lower trough levels in children than in adults; infants should be evaluated and LPV dosing adjusted for incremental growth at frequent intervals.

Pediatric dose (age >6 months to 18 years): Given WITHOUT Concomitant EFV, NVP, f-APV, or NFV
Oral Solution
230/57.5 mg/m² given twice daily, not to exceed the recommended adult dose. The recommended weight-based dosing for patients < 15 kg is 12/3 mg/kg given twice daily and the dosage for patients ≥ 15 kg to 40 kg is 10/2.5 mg/kg given twice daily.

NOTE: Use of 230 mg LPV per m² of body surface area in children is associated with AUC LPV levels similar to AUC achieved with standard doses in adults, but is associated with lower trough levels in children than in adults; therefore, some clinicians may opt to initiate therapy with higher doses of LPV/RTV.
Tablets (100 mg LPV/25 mg RTV)
<table>
<tr><th>Body weight (kg)</th><th>Body surface area (m²)*</th><th>Number of tablets given twice-daily</th></tr>
<tr><td>15 to 25 kg</td><td>>0.6 to <0.9</td><td>2</td></tr>
<tr><td>>25 to 35 kg</td><td>>0.9 to <1.4</td><td>3</td></tr>
<tr><td>>35 kg</td><td>>1.4</td><td>4 (or two 200 mg LPV/50 mg RTV adult tablets)</td></tr>
</table>
Pediatric dose (age >6 months to 18 years):
Concomitant Therapy: Efavirenz, Nevirapine, (Fos)amprenavir, or Nelfinavir
Oral Solution
A dose increase to 300/75 mg/m² is needed, not to exceed the recommended adult dose. If weight-based dosing is preferred, the recommended dosage for patients <15 kg is 13/3.25 mg/kg given twice daily and the dosage for patients >15 kg to 45 kg is 11/2.75 mg/kg given twice daily.

NOTE: Use of 300 mg per m² of body surface area in children (when coadministered with NVP, EFV, f-APV, or NFV) is associated with AUC LPV levels similar to AUC achieved with standard doses in adults, but it is associated with lower trough levels in children than in adults; therefore, some clinicians may choose to initiate therapy with high doses of LPV/RTV
</td></tr>
</table>

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<table>
<tr><th>Drug Age
[Pediatric Approval by US FDA]</th><th>Formulation</th><th>Dose</th></tr>
<tr><td></td><td></td><td>Tablets
<table>
<tr><th>Body weight (kg)</th><th>Body surface area (m^2)*</th><th>Number of tablets given twice daily</th></tr>
<tr><td>15 to 20 kg</td><td>>0.6 to <0.8</td><td>2</td></tr>
<tr><td>>20 to 30 kg</td><td>>0.8 to <1.2</td><td>3</td></tr>
<tr><td>>30 to 45 kg</td><td>>1.2 to <1.7</td><td>4 (or two 200 mg LPV/50 mg RTV tablets)</td></tr>
<tr><td>>45 kg</td><td>>1.7</td><td>4 or 6 (or two or three 200 mg LPV/50 mg RTV adult tablets)</td></tr>
</table>
*Oral solution is available for children with a BSA less than 0.6 m^2 or those who are unable to reliably swallow a tablet.</td></tr>
<tr><td>Atazanavir (ATV) 6-18 years [2003]</td><td>• Capsules 100 mg, 150 mg, 200 mg, and 300 mg</td><td>Neonatal/Infant dose:
Not approved for use in neonates/infants. Should not be administered to infants <3 months of age due to the risks associated with hyperbilirubinemia (kernicterus).
Pediatric dose (age 6-18 years):
Both ATV and RTV to be taken once daily with food.
Recommended dose in treatment-naïve patients:
<table>
<tr><th>Weight (kg)</th><th>ATV dose</th><th>RTV dose</th></tr>
<tr><td>15-<25</td><td>150 mg</td><td>80 mg</td></tr>
<tr><td>25-<32</td><td>200 mg</td><td>100 mg</td></tr>
<tr><td>32-<39</td><td>250 mg</td><td>100 mg</td></tr>
<tr><td>≥39</td><td>300 mg</td><td>100 mg</td></tr>
</table>
For treatment—naive pediatric patients of age >13 years and weight >39 kg who do not tolerate RTV: may use ATV 400 mg given once daily (without RTV) with food. However, if unboosted ATV is used, higher doses (on a per kg or m^2 basis) are required to achieve the target drug levels.
Recommended dose in treatment-experienced patients:
<table>
<tr><th>Weight (kg)</th><th>ATV dose</th><th>RTV dose</th></tr>
<tr><td>25-<32</td><td>200 mg</td><td>100 mg</td></tr>
<tr><td>32-<39</td><td>250 mg</td><td>100 mg</td></tr>
<tr><td>≥39</td><td>300 mg</td><td>100 mg</td></tr>
</table></td></tr>
</table>

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<table>
<tr><th>Drug Age
[Pediatric Approval by US FDA]</th><th>Formulation</th><th>Dose</th></tr>
<tr><td>Fosamprenavir (fAMP) 2-18 years [2007]</td><td>• Oral Suspension 50 mg/ml (prodrug, equivalent to 43 mg APV/ml)
• Tablet 700 mg f-APV calcium (prodrug, equivalent to 600 mg APV)</td><td>Neonate/Infant dose: Not approved for use in neonates/infants.
Pediatric dose (age 2-18 years):
Once daily dosing is not recommended for pediatric patients.
• Antiretroviral-naïve patient (age 2-5 years): 30 mg/kg (max dose 1400 mg) twice daily.
• Antiretroviral-naïve patient (age ≥6 years): 30 mg/kg (max.dose 1400 mg) twice daily (without RTV) OR 18 mg/kg (max.dose 700 mg) + RTV 3 mg/kg (max. dose 100 mg) twice daily.
• Antiretroviral-experienced patients (age >6 years): 18 mg/kg (max.dose 700 mg) + RTV 3 mg/kg (max. dose 100 mg) twice daily.
Note: When administered without RTV, the adult regimen of f-AMP tablets (1,400 mg f-APV twice daily) can be used for patients weighing ≥47 kg OR when administered with RTV, the adult regimen of 700 mg f-APV tablets + 100 mg RTV both given twice daily, can be used in patients weighing ≥ 39 kg. RTV capsules can be used in patients weighing ≥33 kg.</td></tr>
<tr><td>Darunavir (DRV) 6-18 years [2008]</td><td>• Tablet 75 mg, 400 mg, and 600 mg</td><td>Neonatal/infant dose:
Not approved for use in neonates/infants.
Pediatric dose (age <3 years of age): DRV/r should not be used in pediatric patients below 3 years of age.
Pediatric dose (ages 3 to <6 year of age): Safety and efficacy of DRV/r has not been established.
Pediatric (ages 6 to <18 years and weighing atleast 20 kg):
<table><tr><th>Weight (kg)</th><th>Dose (both twice daily with food)</th></tr><tr><td>≥20 to <30 kg</td><td>DRV 375 mg (five 75 mg tablets) + RTV 50 mg (0.6 ml of 80 mg/ml)</td></tr><tr><td>≥30 to <40 kg</td><td>DRV 450 mg (six 75 mg tablets) + RTV 60 mg (0.8 ml of 80 mg/ml)</td></tr><tr><td>≥40 kg</td><td>DRV 600 mg (one 600 mg tablet) + RTV 100 mg (one 100 mg tab)</td></tr></table>Do not use once daily dosing in pediatric patients. DRV tablets should be taken with RTV twice daily with food.
Children should be assessed for the ability to swallow tablets before prescribing DRV.</td></tr>
</table>

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Drug Age [Pediatric Approval by US FDA]	*Formulation*	*Dose*
Tipranavir (TPR) *2-18 years* [2008]	• Liquid 100 mg/ml • Capsule 250 mg	*Neonatal/Infant dose*: Not approved for use in neonates/infants. *Pediatric dose: (age 2-18 years)*: Must be coadministered with ritonavir (RTV). Body surface area dosing: 375 mg TPV per m^2 body surface area per dose coadministered with 150 mg RTV per m^2 body surface area per dose, both twice daily (maximum dose TPV 500 mg + RTV 200 mg twice daily). Weight-based dosing: 14 mg TPV per kg body weight per dose coadministered with 6 mg RTV per kg body weight per dose, both twice daily (maximum dose TPV 500 mg + RTV 200 mg twice daily). NOTE: For patients with intolerance or toxicity and who do not have virus resistant to multiple PIs, a dose reduction can be considered: Body surface area dosing: 290 mg TPV per m^2 body surface area per dose coadministered with 115 mg RTV per m^2 body surface area per dose, both twice daily. Weight-based dosing: 12 mg TPV per kg body weight per dose coadministered with 5 mg RTV per kg body weight per dose, both twice daily.
Enfuvirtide (T20) *6-18 years* [2003]	• Lyophilized powder for injection 90 mg/1 ml when reconstituted	*Neonatal/Infant dose*: Not approved for use in neonates/infants. *Pediatric/adolescent dose (age 6-16 years)*: 2 mg per kg of body weight (maximum dose, 90 mg [1 ml]) given twice daily, injected subcutaneously into the upper arm, anterior thigh, or abdomen. (see weight table below) *Adolescent (age >16 years)/Adult dose*: 90 mg (1ml) twice-daily injected subcutaneously into the upper arm, anterior thigh, or abdomen.

Weight (kg)	Dose per bid injection	Injection volume (90 mg/ml)
11.0 to15.5	27	0.3 ml
15.6 to 20.0	36	0.4 ml
20.1 to 24.5	45	0.5 ml
24.6 to 29	54	0.6 ml
29.1 to 33.5	63	0.7 ml
33.6 to 38	72	0.8 ml
38.1 to 42.5	81	0.9 ml
≥42.5	90	1.0 ml

*The Australian Therapeutics Goods Administration (TGA) has granted orphan status to TDF for pediatric use, for patients aged between two and 17 years of age. It is available in oral powder (40 mg/1g) and tablet (300 mg) formulations.

**May not be widely available

Table 1.4.3: Fixed-dose antiretroviral formulations for children

Drug Age [Pediatric Approval by US FDA]	*Formulation*	*Dose*	
Triomune Baby/Junior (Stavudine 6/12 mg + lamivudine 30/60 mg + nevirapine 50/100 mg) <*30 kg* [2007]	Dispersible tablet	**Weight band**	**Dose**
		3 to <6	1 tablet Triomune Baby bid
		6 to <10	1½ tablets Triomune Baby bid
		10 to <15	1 tablet Triomune Junior bid
		15 to <20	1 tablet Triomune Junior am, and 1½ tablets Triomune Junior pm
		20 to <25	1½ tablets Triomune Junior bid
		25 to <30	2 tablets Triomune Junior bid
		Note: Prior to initiating therapy with Triomune Baby/Junior, lead-in dosing is required for nevirapine	
Lamivir-S Baby/Junior (Stavudine 6/12 mg + lamivudine 30/60 mg)< *30kg* [2008]	Dispersible tablet	**Weight band**	**Dose**
		3 to <6	1 tablet Lamivir-S Baby bid
		6 to <10	1½ tablets Lamivir-S Baby bid
		10 to <15	1 tablet Lamivir-S Junior bid
		15 to <20	1 tablet Lamivir-S Junior am, and 1½ tablets Lamivir-S Junior pm
		20 to <25	1½ tablets Lamivir-S Junior bid
		25 to <30	2 tablets Lamivir-S Junior bid

comprehensive updated information. A brief overview of PK and PD interactions follows.

Pharmacokinetic Interactions

Optimal absorption may depend on factors such as the presence or absence of food and pH of the gut. Drug-food interactions with antiretrovirals are listed in (Table 1.4.5) In infants and children, hydrochloric acid production may be greater or less than that seen in adults, depending on age. Thus, absorption of antiretrovirals in this patient population is unpredictable and the true magnitude of interactions with agents that alter gastric pH in infants and children is unknown. Atazanavir absorption is highly pH dependent. H_2 antagonists and proton pump inhibitors reduce atazanavir absorption.

Metabolic interactions are a major concern in HIV therapy. CYP3A4 is the most abundant isoform in human liver, and metabolizes approximately 60 percent of the therapeutic drugs. Most PIs and NNRTIs are CYP3A4 substrates. Therefore, inhibition or induction of this enzyme is of concern. For infants, children, and adolescents, the metabolic capacity of the liver can vary from <10 percent to >160 percent of adult values, depending on age and the enzyme. Thus, interactions may be of a greater or lesser magnitude in HIV infected children.

For example, efavirenz induces CYP3A4. Anticonvulsant concentrations must be carefully monitored in children taking efavirenz. Rifampicin is a more potent inducer of CYP3A4 than efavirenz. Rifampicin is contraindicated with all PIs, whether boosted or unboosted, because of the significant reduction, usually >75 percent, in PI concentrations. Rifampicin also decreases nevirapine and efavirenz concentrations.

Ritonavir inhibits CYP3A4, an inhibition which is used advantageously with most PIs coadministered with ritonavir (PI boosting). However, this property also results in undesirable interactions. Ritonavir increases clarithromycin area under the curve (AUC) by 77 percent and almost completely inhibits formation of its metabolite.

Table 1.4.4: Online interactive databases for antiretroviral drug interactions (accessed November 2009)

http://www.HIV druginteractions.org

A Web site from the Liverpool HIV Pharmacology Group. Site features information on interactions with each class of antiretroviral drugs.

http://www.clinicalcareoptions.com/HIV/Treatmentpercent 20Updates/ARVpercent20Interactions.aspx

A downloadable tool for Palm and Pocket PC/Windows Mobile handheld devices, provided by Clinical Care Options. The tool features an interactive database of interactions between antiretrovirals and other medications frequently prescribed for HIV infected patients.

http://hivinsite.ucsf.edu/InSite?page=ar-00-02

HIV InSite's fully referenced searchable database of interactions involving atleast one antiretroviral drug. Provides information regarding effects on drug levels, potential clinical effects, mechanisms of interaction, management tips, and suggested alternative agents.

Table 1.4.5: Drug-food interactions with antiretrovirals approved for pediatric use[8, 9]

NRTIs/NtRTIs

- Didanosine should be administered on an empty stomach (30 minutes before or 2 hours after a meal).
- All other NRTIs (abacavir, emtricitabine, lamivudine, stavudine, zidovudine) can be given without regard to food.

NNRTIs

- Efavirenz should be taken on an empty stomach, preferably at bedtime
- Nevirapine can be given without regard to food.

PIs

- Atazanavir, darunavir, nelfinavir and ritonavir (full dose)* should be administered with food.
- Tipranavir can be given without regard to food.
- For both fosamprenavir and lopinavir/ritonavir, the tablets can be given without regard to food. However, fosamprenavir suspension and lopinavir/ritonavir oral solution should be administered with food.

Entry inhibitors

- Enfuvirtide: NA

**Ritonavir as a pharmacokinetic enhancer:* The major use of RTV is as a pharmacokinetic enhancer of other PIs. The dose of ritonavir recommended varies with the different protease inhibitors. See dosing information for specific PI.

Some other commonly used drugs that interact with antiretrovirals are carbamazepine, phenytoin, fluconazole, itraconazole, warfarin, cisapride, pimozide, midazolam, triazolam, ergot alkaloids, simvastatin, lovastatin and St John's wort.

Renal interactions may be the result of alterations in glomerular filtration or inhibition of tubular secretion. NRTIs, except zidovudine, are highly dependent on renal function for drug elimination.

Pharmacodynamic Interactions

Antiretrovirals are combined for additive or synergistic effects against HIV. However, some drugs cannot be combined because of antagonistic effects or additive toxicity.

Table 1.4.6 lists key PD drug interactions with antiretrovirals.

Barriers to Treatment

Despite the benefits, for the vast majority of the world's HIV infected children, HAART is inaccessible and only 5-7 percent of HIV infected patients receiving HAART are children. Barriers to the widespread use of HAART in children include: [3,21]

Table 1.4.6: Key pharmacodynamic drug interactions that preclude the use of the two drugs

Drug-drug interaction	*Comment*
Stavudine and zidovudine	Zidovudine has a greater affinity for thymidine kinase, which facilitates the initial intracellular phosphorylation of both drugs
Stavudine and didanosine	Increased risk of peripheral neuropathy, lactic acidosis and pancreatitis
Didanosine and tenofovir	PK interaction that increases didanosine concentrations and an apparent PD interaction that results in high rates of early virologic failure and CD4 cell toxicity

- Lack of assays to diagnose HIV infection in infants aged <18 months
- the limited number of pediatric drug formulations; palatability issues
- limited pediatric pharmacokinetic and pharmacodynamic data
- the lack of effective follow-up programs for infected children
- poor on-the-ground expertise in managing HAART in children.

Future Treatment/Novel Therapies

A number of novel two-and three-drug combinations for children, such as abacavir/lamivudine, zidovudine/lamivudine, abacavir/lamivudine/nevirapine and zidovudine/lamivudine/nevirapine are currently in development. Novel formulations such as lopinavir/ritonavir sprinkles are also in development for pediatric use. Several studies that are scheduled to begin in 2010 will evaluate the efficacy and safety of these treatments in HIV infected children. Availability of these formulations will improve adherence and expand treatment options.

Pediatric studies are also currently under way to determine the safety and efficacy of antiretroviral agents such as etravirine and tenofovir.

NRTIs in development for adult use include elvicitabine, racivir and apricitabine. Rilpivirine is a second generation NNRTI under study. Sifuvirtide is a next-generation fusion inhibitor in development. Experimental chemokine receptor inhibitors include the CCR5 antagonist vicriviroc and CXCR4 antagonists. Elvitegravir is a once daily integrase inhibitor being studied in adults. Ibalizumab is an anti-CD4 monoclonal antibody that interferes with HIV viral entry. New classes of ART under investigation include inhibitors of viral transcription, translation and maturation.[4]

The future, thus, appears bright.

Table 1.4.7: Major toxicities of antiretrovirals[8,9]

Antiretroviral	*Major toxicities*
NRTIs	
Abacavir	*More common:* Nausea, vomiting, fever, headache, diarrhea, rash, and anorexia. *Less common (more severe):* Serious and sometimes fatal hypersensitivity reactions have been associated with ABC: approximately 5 percent of adults and children (rate varies by race/ethnicity) receiving ABC develop a potentially fatal hypersensitivity reaction. *Rare:* Increased liver enzymes, elevated blood glucose, elevated triglycerides, and possible increased risk of myocardial infarction.
Didanosine	*More common:* Diarrhea, abdominal pain, nausea, and vomiting. *Less common (more severe):* Peripheral neuropathy (dose related, more common in patients with advanced disease), electrolyte abnormalities, and hyperuricemia; Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases; Pancreatitis, increased liver enzymes, and retinal depigmentation, retinal changes, and optic neuritis; Hepatic toxicity and hepatic failure; Fat redistribution.
Emtricitabine	*More common:* Headache, insomnia, diarrhea, nausea, rash, and skin discoloration (hyperpigmentation on palms and/or soles, predominantly observed in non-Caucasian patients). *Less common (more severe):* Neutropenia; Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases; Exacerbations of hepatitis have occurred in HIV/HBV coinfected patients when changes have been made from FTC-containing regimens to non-FTC-containing regimens.
Lamivudine	*More common:* Headache, fatigue, and nausea, which generally decrease over time; decreased appetite, diarrhea, skin rash, and abdominal pain. *Less common (more severe):* Pancreatitis (primarily seen in children with advanced HIV infection receiving other additional medications), peripheral neuropathy, anemia, decreased neutrophil count, increased liver enzymes, and fat redistribution; Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases; Exacerbations of hepatitis have occurred in HIV/HBV coinfected patients when changes have been made from 3TC-containing regimens to non-3TC-containing regimens.
Stavudine	*More common:* Headache, gastrointestinal disturbances, skin rashes, and lipoatrophy. *Less common (more severe):* Peripheral neuropathy, pancreatitis, and lipodystrophy/lipoatrophy; Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases; The combination of d4T with didanosine (ddI) may result in enhanced toxicity (increased risk of fatal and non-fatal cases of lactic acidosis or pancreatitis). *Rare:* Increased liver enzymes; rapidly progressive ascending neuromuscular weakness.
Zidovudine	*More common:* Hematologic toxicity, including granulocytopenia and anemia; Headache, malaise, nausea, vomiting, and anorexia. *Less common (more severe):* Myopathy (associated with prolonged use), myositis, and liver toxicity; Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases; Fat redistribution. *Rare:* Increased risk of hypospadias after first trimester exposure to ZDV observed in one cohort study.
NNRTIs	
Efavirenz	*More common:* Skin rash; increased transaminase levels; Central nervous system abnormalities (e.g. somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, euphoria) primarily reported in adults. *Rare:* In cynomolgus monkeys, prenatal EFV exposure has been associated with central nervous system congenital abnormalities in infant monkeys. Based on these data and retrospective reports in humans, EFV has been classified as FDA Pregnancy Class D (positive evidence of human fetal risk). EFV use in the first trimester of pregnancy should be avoided and women of childbearing potential should undergo pregnancy testing as well as counseling about the risk to the fetus and need to avoid pregnancy before initiating EFV therapy.
Nevirapine	*More common:* Skin rash (some severe and requiring hospitalization; some life-threatening, including Stevens-Johnson syndrome and toxic epidermal necrolysis), fever, nausea, headache, and abnormal hepatic transaminases. NVP should be permanently discontinued and not restarted in children or adults who develop severe rash, rash with constitutional symptoms, or rash with elevated hepatic transaminases. *Less common (more severe):* Severe, life-threatening, and in rare cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure (these are less common in children than adults). The majority of cases occur in the first 12 weeks of therapy. May be associated with rash or other signs or symptoms of hypersensitivity reaction. Risk factors for NVP-related hepatic toxicity in adults include: baseline elevation in serum transaminase levels, hepatitis B or C infection, female gender, and higher CD4 count at time of therapy initiation (CD4 count >250 cells/mm^3 in adult females and >400 cells/mm^3 in adult males). Hypersensitivity reactions have been reported, including, but not limited to, severe rash or rash accompanied by fever, blisters, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise, and significant hepatic abnormalities. NVP should be permanently discontinued and not restarted in children or adults who develop symptomatic hepatitis, severe transaminase elevations, or hypersensitivity reactions.

Contd...

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Antiretroviral	*Major toxicities*
PIs	
Amprenavir	
Atazanavir	*More common:* Asymptomatic elevations in indirect bilirubin, jaundice, headache, fever, arthralgia, depression, insomnia, dizziness, nausea, vomiting, diarrhea, and paresthesias. *Less common (more severe):* Prolongation of PR interval of electrocardiogram; Abnormalities in AV conduction generally limited to first-degree AV block, but with rare reports of second-degree AV block; Rash, generally mild to moderate, but in rare cases include life-threatening Stevens–Johnson syndrome; Fat redistribution and lipid abnormalities may be less common than with other PIs. *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, and elevation in serum transaminases. Nephrolithiasis. Hepatotoxicity (patients with hepatitis B or C are at increased risk).
Darunavir	*More common:* Diarrhea, nausea, vomiting, abdominal pain, headache, and fatigue. *Less common:* Skin rash, including erythema multiforme and Stevens-Johnson syndrome; Fever and elevated hepatic transaminases; Lipid abnormalities. *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs; Hepatic dysfunction, particularly in patients with underlying risk factors (e.g. hepatitis B or hepatitis C virus coinfection, baseline elevation in transaminases).
Fosamprenavir	*More common:* Vomiting, nausea, diarrhea, perioral paresthesias, headache, rash, and lipid abnormalities. *Less common (more severe):* Life-threatening rash, including Stevens-Johnson syndrome, in <1 percent of patients; Fat redistribution, neutropenia, and elevated serum creatinine kinase levels. *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, hemolytic anemia, and elevation in serum transaminases.
Lopinavir/ritonavir	*More common:* Diarrhea, headache, asthenia, nausea and vomiting, and rash in patients receiving LPV/RTV with other antiretroviral drugs; lipid abnormalities. *Less common (more severe):* Fat redistribution. *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, hemolytic anemia, spontaneous bleeding in hemophiliacs, pancreatitis, elevation in serum transaminases, and hepatitis (life-threatening in rare cases).
Nelfinavir	*More common:* Diarrhea (most common); Asthenia, abdominal pain, rash, and lipid abnormalities. *Less common (more severe):* Exacerbation of chronic liver disease; Fat redistribution. *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, and elevation in serum transaminases.
Ritonavir	*More common:* Nausea, vomiting, diarrhea, headache, abdominal pain, anorexia, circumoral paresthesias, lipid abnormalities. *Less common (more severe):* Exacerbation of chronic liver disease; fat redistribution. *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, pancreatitis, and hepatitis (life-threatening in rare cases); Allergic reactions, including bronchospasm, urticaria, and angioedema; Prolongation of the PR interval and second or third degree atrioventricular block.
Tipranavir	*More common:* Diarrhea, nausea, fatigue, headache, rash (more frequent in children than adults), and vomiting; Laboratory abnormalities are elevated liver enzymes, cholesterol, and triglycerides. *Less common (more severe):* Fat redistribution; Clinical hepatitis and hepatic decompensation, including some fatalities; Patients with chronic hepatitis B or C coinfection or elevations in transaminases are at increased risk for developing further transaminase elevations or hepatic decompensation (approximately 2.5-fold risk); Epistaxis. *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs; Possible association with increased risk of intracranial hemorrhage.
Fusion inhibitor	
Enfuvirtide	*Most common:* Almost all patients (87-98 %) experience local injection site reactions including pain and discomfort, induration, erythema, nodules and cysts, pruritis, and ecchymosis; Usually mild to moderate in severity but can be more severe. *Less common:* Increased rate of bacterial pneumonia (unclear association) and local site cellulitis (3-8%). *Rare:* Hypersensitivity reactions (<1%) including fever, nausea and vomiting, chills, rigors, hypotension, elevated liver transaminases; Immune-mediated reactions including primary immune complex reaction, respiratory distress, glomerulonephritis, and Guillain-Barre syndrome; Patients experiencing hypersensitivity reactions should seek immediate medical attention. Therapy should not be restarted in patients with signs and symptoms consistent with hypersensitivity reactions.

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SECTION II

Clinical Manifestations of HIV Infection in Children

2.1

Clinical Manifestations of HIV/AIDS in Children: An Overview

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The threat of Human Immunodeficiency Virus/Acquired Immuno Deficiency Syndrome (HIV/AIDS) is a major menace that faces mankind, with a huge global impact permeating the social, cultural and economic sectors of all nations. The global impact of this epidemic has been so dramatic and devastating that it has been described as the "epidemic of our century". In developed countries, children constitute 2 percent, whereas in Asia and Africa, they comprise 15 to 20 percent of all HIV infected patients, due to greater affliction of women in the childbearing age.[1]

In contrast to developed nations, malnutrition and infections are the main factors that influence the progression of HIV/AIDS in resource poor countries. For example, measles, varicella, Pneumocystis pneumonia (PCP), tuberculosis, and acute persistent diarrhea due to opportunistic gut pathogens contribute to early mortality. Neurological manifestations are also common and multifactorial in etiology. Thus, the clinical presentation of pediatric AIDS in Asia has unique features that distinguish it from HIV related disease noted in North America and Europe.

Clinical manifestations in children differ from those in adults due to poorly developed immunity that allows greater dissemination throughout various organs, particularly the central nervous system (CNS). The pattern of disease progression may be: (a) Rapid—consisting of infants who manifest within the first few months of life and who have a rapid downhill course, (b) Intermediate—manifesting between 2 to 5 years, with persistent generalized lymphadenopathy, hepatosplenomegaly and recurrent bacterial infections including tuberculosis and (c) Late—revealing minor manifestations later in childhood or those who may be asymptomatic and detected incidentally.[2]

Clinical Classification of HIV Infected Children

In 1994, The Centers for Disease Control and Prevention (CDC) published a revised classification system for HIV infection in children less than 13 years of age.[3] The classification system categorizes the stage of pediatric disease using two parameters: clinical status and degree of immunological impairment. Once classified, a child cannot be reclassified into a less severe category, even if the clinical or immunological status improves. Clinical categories for children are identified as N, A, B, C, or death (Table 2.1.1).

Table 2.1.1: Clinical categories for children younger than 13 years of age with HIV infection

Category N: Not symptomatic
Children who have no signs or symptoms considered to be the result of HIV infection or have only 1 of the conditions listed in category A.
Category A: Mildly symptomatic
Children with 2 or more of the conditions listed but none of the conditions listed in categories B and C.
• Lymphadenopathy (≥0.5 cm at more than 2 sites; bilateral at 1 site)
• Hepatomegaly
• Splenomegaly
• Dermatitis
• Parotitis
• Recurrent or persistent upper respiratory tract infection, sinusitis, or otitis media
Category B: Moderately symptomatic
Children who have symptomatic conditions other than those listed for category A or C that are attributed to HIV infection.
• Anemia (hemoglobin <8 g/dL [<80 g/L]), neutropenia (white blood cell count <1,000/mL [$<1.0 \times 10^9$/L]), and/or thrombocytopenia (platelet count $<100 \times 10^3$/mL [$<100 \times 10^9$/L]) persisting for ≥30 days
• Bacterial meningitis, pneumonia, or sepsis (single episode)
• Candidiasis, oropharyngeal (thrush), persisting (>2 months) in children older than 6 months of age
• Cardiomyopathy
• Cytomegalovirus infection, with onset before 1 month of age
• Diarrhea, recurrent or chronic
• Hepatitis

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Category B: Moderately symptomatic
• Herpes simplex virus (HSV) stomatitis, recurrent (>2 episodes within 1 year) • HSV bronchitis, pneumonitis, or esophagitis with onset before 1 month of age • Herpes zoster (shingles) involving at least 2 distinct episodes or more than 1 dermatome • Leiomyosarcoma • Lymphoid interstitial pneumonia or pulmonary lymphoid hyper plasia complex • Nephropathy • Nocardiosis • Persistent fever (lasting >1 month) • Toxoplasmosis, onset before 1 month of age • Varicella, disseminated (complicated chickenpox)
Category C: Severely symptomatic
• Serious bacterial infections, multiple or recurrent (i.e. any combination of at least 2 culture-confirmed infections within a 2 years period), of the following types: septicemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media, superficial skin or mucosal abscesses, and indwelling catheter-related infections) • Candidiasis, esophageal or pulmonary (bronchi, trachea, lungs) • Coccidioidomycosis, disseminated (at site other than or in addition to lungs or cervical or hilar lymph nodes) • Cryptococcosis, extrapulmonary • Cryptosporidiosis or isosporiasis with diarrhea persisting>1 month • Cytomegalovirus disease with onset of symptoms after 1 month of age (at a site other than liver, spleen, or lymph nodes) • Encephalopathy (at least 1 of the following progressive findings present for at least 2 months in the absence of a concurrent illness other than HIV infection that could explain the findings): 1. failure to attain or loss of developmental milestones or loss of intellectual ability, varied by standard developmental scale or neuropsychologic tests; 2. impaired brain growth or acquired microcephaly demonstrated by head circumference measurements or brain atrophy demonstrated by CT or MRI (serial imaging required for children younger than 2 years of age); or 3. acquired symmetric motor deficit manifested by 2 or more of the following: paresis, pathologic reflexes, ataxia, or gait disturbance • HSV infection causing a mucocutaneous ulcer that persists for greater than 1 month or bronchitis, pneumonitis or esophagitis for any duration affecting a child older than 1 month of age • Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes) • Kaposi's sarcoma • Lymphoma, primary, in brain • Lymphoma, small, noncleaved cell (Burkitt), or immunoblastic; or large-cell lymphoma of B-lymphocyte or unknown immunologic phenotype • *Mycobacterium tuberculosis* infection, disseminated or extra-pulmonary • *Mycobacterium*, other species or unidentified species infection, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes) • *Pneumocystis jirovecii* pneumonia

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Category C: Severely symptomatic
• Progressive multifocal leukoencephalopathy • Salmonella (nontyphoid) septicemia, recurrent • Toxoplasmosis of the brain with onset at after 1 month of age • Wasting syndrome in the absence of a concurrent illness other than HIV infection that could explain the following findings: 1. persistent weight loss >10 percent of baseline; 2. downward crossing of at least 2 of the following percentile lines on the weight-for-age chart (e.g., 95th, 75th, 50th, 25th, 5th) in a child 1 year of age or older; OR 3. <5th percentile on weight-for-height chart on 2 consecutive measurements, ≥30 days apart; PLUS 1. chronic diarrhea (i.e. at least 2 loose stools per day for >30 days); OR 2. documented fever (for >30 days, intermittent or constant)

Modified from the Centers for Disease Control and Prevention. 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age. Official authorized addenda: Human immunodeficiency virus infection codes and official guidelines for coding and reporting ICD-9-CM.MMWR Recomm Rep 1994;43(RR- 12):1ndash;19.

The immune classification is based on the absolute CD4+ lymphocyte count or the percentage of CD4+ cells (Table 2.1.2). The adjustment of the absolute CD4+ count with age is necessary as counts that are relatively high in normal infants decline steadily until 6 years of age.

The clinical staging and case definition of HIV for resource-constrained settings were developed by the WHO in 1990 and revised in 2006.[4] Staging is based on clinical findings that guide the diagnosis, evaluation, and management of HIV/AIDS, and does not require a CD4+ cell count. This staging system is used in many countries to determine eligibility for antiretroviral therapy (ART). Clinical stages are categorized as 1 through 4, progressing from primary HIV infection to advanced HIV/AIDS (Table 2.1.3). These stages are defined by specific clinical conditions or symptoms.

Clinical Manifestations

The clinical manifestation of HIV infection varies widely among infants, children and adolescents. In one of the earliest Indian studies by Merchant et al[1] the most common early symptoms were protein energy malnutrition, hepatosplenomegaly, recurrent or persistent diarrhea and persistent generalized lymphadenopathy (the presence of enlarged lymph nodes, >1 cm, in two or more extrainguinal sites for more than 3 months without an apparent cause). In a Zambian study, Siziya reported weight loss, generalized lymphadenopathy, chronic watery diarrhea and chronic chest infection as common manifestations.[5]

The age at which infection occurs influences the presentation of the disease. It has been suggested that if

intrauterine infection coincides with the period of rapid expansion of CD4+ cells in the fetus, it could infect the majority of the body's immunocompetent cells. The migration of these cells to the marrow, spleen, and thymus results in efficient systemic delivery of HIV virus which is unchecked by the immature immune system of the fetus. Thus infection would be established before development of the immune system making HIV a multisystem disorder with a wide variety of clinical signs and symptoms.[1, 6] A congenital HIV syndrome, encompassing microcephaly, a prominent box-like forehead, flattened nasal bridge, short nose with flattened columella, well formed triangular philtrum and patulous lips with prominent upper vermilion border has been described, but its specificity to HIV infection is poor (Table 2.1.4).[2]

The various manifestations of HIV/AIDS can be categorized by their effects on the human organ systems. The authors have made an attempt to give the salient information in a nutshell in this chapter, but the readers are requested to go through the specific chapters on HIV related manifestations pertaining to each organ system for more details.

Table 2.1.2: Pediatric HIV classification for children younger than 13 years

Immunologic categories										
Age-specific CD4+ T-lymphocyte count percentage of total lymphocytes*							Clinical Classifications†			
	<12 month		1-5 year		6-12 year					
Immunologic definitions	Cells/mm³	%	Cells/mm³	%	Cells/mm³	%	N: No signs or symptoms	A: Mild signs and symptoms	B: Moderate signs and symptoms‡	C: Severe signs and symptoms‡
1. No evidence of suppression	≥1500	≥25	≥1000	≥25	≥500	≥25	N1	A1	B1	C1
2. Evidence of moderate – suppression	750-1499	15-24	500-999	15-24	200-499	15-24	N2	A2	B2	C2
3. Severe suppression	<750	<15	<500	<15	<200	<15	N3	A3	B3	C3

Modified from the Centers for Disease Control and Prevention: 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age. Official authorized addenda: Human immunodeficiency virus infection codes and official guidelines for coding and reporting ICD-9-CM.MMWR Recomm Rep 1994;43(RR-12):1-19. Red Book: 2006 Report of the Committee on Infectious Diseases, 27th ed. Elk Grove Village, IL, American Academy of Pediatrics, 2006, p 382.

* To convert values in μL to Système International units (×10⁹/L), multiply by 0.001.

† Children whose HIV infection status is not confirmed are classified by using this grid with a letter E (for perinatally exposed) placed before the appropriate classification code (e.g. EN2).

‡ Lymphoid interstitial pneumonitis in category B or any condition in category C is reportable to state and local health departments as acquired immunodeficiency syndrome (AIDS-defining conditions).

Table 2.1.3: WHO clinical staging of HIV/AIDS for children with confirmed HIV infection

Clinical stage 1

- Asymptomatic
- Persistent generalized lymphadenopathy

Clinical stage 2

- Unexplained persistent hepatosplenomegaly
- Papular pruritic eruptions
- Extensive wart virus infection
- Extensive molluscum contagiosum
- Fungal nail infections
- Recurrent oral ulcerations
- Unexplained persistent parotid enlargement
- Lineal gingival erythema
- Herpes zoster

Contd...

Contd...

- Recurrent or chronic upper respiratory tract infections (otitis media, otorrhea, sinusitis or tonsilitis)

Clinical stage 3

- Unexplained[a] moderate malnutrition not adequately responding to standard therapy
- Unexplained persistent diarrhea (14 days or more)
- Unexplained persistent fever (above 37.5°C intermittent or constant, for longer than one month)
- Persistent oral candidiasis (after first 6-8 weeks of life)
- Oral hairy leukoplakia
- Acute necrotizing ulcerative gingivitis or periodontitis
- Lymph node tuberculosis
- Pulmonary tuberculosis
- Severe recurrent bacterial pneumonia
- Symptomatic lymphoid interstitial pneumonitis

Contd...

Contd...

- Chronic HIV associated lung disease including bronchiectasis
- Unexplained anemia (<8 mg/dl), neutropenia (<0.5 x 10^9/L) and/ or chronic thrombocytopenia (<50 x 10^9/L)

***Clinical stage 4**[b]*

- Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy
- Pneumocystis pneumonia
- Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection or meningitis but excluding pneumonia)
- Chronic herpes simplex infection (orolabial or cutaneous of more than one month's duration or visceral at any site)
- Extrapulmonary tuberculosis
- Kaposi sarcoma
- Esophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
- Central nervous system toxoplasmosis (after one month of life)
- HIV encephalopathy
- Cytomegalovirus infection: retinitis or cytomegalovirus infection affecting another organ, with onset at age older than one month
- Extrapulmonary cryptococcosis (including meningitis)
- Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis)
- Chronic cryptosporidiosis
- Chronic isosporiasis
- Disseminated nontuberculous mycobacterial infection
- Cerebral or B cell non-Hodgkin's lymphoma
- Progressive multifocal leukoencephalopathy
- Symptomatic HIV associated nephropathy or HIV associated cardiomyopathy

a. Unexplained refers to where the condition is not explained by other causes.

b. Some additional specific conditions can also be included in regional classifications (such as reactivation of American trypanosomiasis [meningoencephalitis and/or myocarditis] in the WHO Region of the Americas, penicilliosis in Asia and HIV associated rectovaginal fistula in Africa).

Source: World Health Organization, WHO Case Definitions of HIV for Surveillance and Revised Clinical Staging and Immunological Classification of HIV related disease in Adults and Children, August 7, 2006.

Table 2.1.4: Presumptive diagnosis of severe HIV disease in infants <18 months. Clinical criteria for presumptive diagnosis of severe HIV disease in infants and children less than 18 months of age requiring ART in situations where virological testing is not available

A presumptive diagnosis of severe HIV disease should be made if:

- The infant is confirmed HIV antibody positive
- Diagnosis of any AIDS-indicator condition(s) can be made
- The infant is symptomatic with two or more of the following:
  - Oral thrush
  - Severe pneumonia
  - Severe sepsis

Other factors that support the diagnosis of severe HIV disease in an HIV seropositive infant include:

Contd...

Contd...

- Recent HIV related maternal death; or advanced HIV disease in the mother
- CD4+ < 20 %

Confirmation of the diagnosis of HIV infection should be sought as soon as possible.

Notes: As per Integrated Management of Childhood Illness (IMCI) definition:

1. Oral thrush: Creamy white to yellow soft small plaques on red or normally colored mucosa which can often be scraped off (pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender. Not responding to topical antifungal treatment.
2. Severe pneumonia: Cough or difficult breathing in a child with chest indrawing, stridor or any of the IMCI general danger signs i.e. lethargic or unconscious, not able to drink or breastfeed, vomiting, and presence or history of convulsions during current illness; responding to antibiotics.
3. Severe sepsis: Fever or low body temperature in a young infant with any severe sign such as fast breathing, chest indrawing, bulging fontanelle, lethargy, reduced movement, not feeding or sucking breast milk, convulsions, etc.

It is unclear how often CD4+ is lowered in the above condition in HIV uninfected children.

Source: Antiretroviral therapy of HIV infection in infants and children in resource-limited settings, towards universal access: Recommendations for a public health approach (2006 revision) WHO 2006 ART of HIV infection in infants and children in RL settings. FINAL VERSION February 2006.

Respiratory System

Pulmonary disease continues to be the major cause of morbidity and mortality in infants and children with HIV/ AIDS. Diagnosis and management is often difficult in resource-limited settings because most HIV related pulmonary disease presents in infancy or early childhood. Recurrent upper respiratory tract infections such as otitis media and sinusitis are usually caused by *Streptococcus pneumoniae*, and *Haemophilus influenzae*. However, unusual pathogens such as *Pseudomonas aeruginosa*, *Candida albicans*, *Moraxella catarrhalis*, and anaerobes are often noted.

The most common pulmonary complication of pediatric HIV infection in the developed world is considered to be PCP. In contrast, in countries where tuberculosis (TB) is endemic, pulmonary TB far exceeds PCP or Lymphoid Interstitial Pneumonitis (LIP). The development of chronic lung disease is common in HIV infected children and may result from recurrent or persistent pneumonia due to bacterial, mycobacterial, viral, fungal or mixed infections. Many abnormalities of large and small airways as well as pulmonary parenchyma can produce chronic cough. Nevertheless, underlying cardiac disease should always be considered in the differential diagnosis of respiratory problems in HIV infected children.

Common lung diseases in HIV infected children may be classified by etiology. Infectious causes include bacteria such as *M. tuberculosis* and *S. pneumoniae*, fungi such as *P. jirovecii* and *C. neoformans*, viruses such as cytomegalovirus and Epstein-Barr Virus, and parasites such as *T. gondii* and *S. stercoralis*. Other less common causes may be neoplasms, pulmonary lymphoid hyperplasia, or lymphoid interstitial pneumonia (LIP).

LIP is the most common lymphoproliferative, non-infectious pulmonary disease in HIV infected patients. It is a distinctive marker of pediatric HIV and may be the first clinical manifestation of the infection in children. It usually occurs in older children in contrast to PCP which is seen in infancy. It is considered a Category B condition according to the CDC Classification and it indicates an HIV related immunological deficit. LIP describes a spectrum of disorders that involve pulmonary lymphocytic infiltrates with mature CD8+ T lymphocytes, plasma cells and histiocytes in the interstitial lung parenchyma, alveolar septa and along the lymphatic vessels with hyperplasia of the pulmonary lymphoid tissue, termed Pulmonary Lymphoid Hyperplasia (PLH). While the specific cause is still yet to be ascertained, it seems to be related to the presence of HIV gene products and pathogens as well as host response mechanisms. Epstein-Barr Virus is thought to have a possible role in its pathogenesis.

LIP can present with a spectrum of clinical manifestations ranging from asymptomatic disease to severe pulmonary insufficiency. The disease is often insidious in onset and slowly progressive, usually occurring during the second or third year of life. Features such as mild cough, dyspnea, chronic parotid enlargement, generalized lymphadenopathy, hepatosplenomegaly and clubbing may be present. The natural history of the disease varies, as it may spontaneously resolve or worsen, but it is generally benign with a favorable prognosis. The development of LIP is well correlated with serum IgG levels greater than 2500 mg/dL. Typical chest radiographic findings reveal bilateral diffuse reticulonodular infiltrates in the lower lobes (Fig. 2.1.1) with enlarged mediastinal or hilar lymph nodes. Chest Computed Tomography (CT) is used to establish the interstitial pattern and also for monitoring the disease, but lung biopsy is the only definite way to confirm the diagnosis.[7]

PCP, a life threatening pulmonary complication, is considered to be the most common AIDS defining condition in children. It is caused by the microorganism *Pneumocystis jirovecii*, formally known as *Pneumocystis carinii*. Primary asymptomatic infection is said to occur in a large number of immunocompetent children by 2-4 years of age, suggested by the presence of serum antibodies to the organism.[8] However, patients at risk are those with advanced HIV infection and impaired cell mediated immunity. The highest incidence is in the first year, peaking between 3-6 months.



Fig. 2.1.1: X-ray chest showing bilateral, diffuse infiltration in LIP

PCP presents acutely as severe pneumonitis, and contributes significantly to morbidity and mortality. Clinical features include tachypnea, cough and respiratory distress, and hypoxia that is less responsive to oxygen administration. Common radiographic abnormalities noted are diffuse bilateral interstitial infiltration and hyperinflation. High resolution CT may reveal abnormalities not detected by chest radiograph, and is therefore a more sensitive and specific investigation. In developing countries, a definitive diagnosis of PCP using techniques such as bronchoalveolar lavage or lung biopsy is seldom performed. In infants and young children where PCP is a common and often fatal illness, a high index of suspicion enables commencement of therapy.[1]

The resurgence of TB worldwide has been mainly due to coexisting HIV infection. TB and HIV seem to be in perfect harmony with each other, each facilitating the other's rapid multiplication, leading to early clinical progression and death.[9] In the presence of such coinfection, children are at an increased risk of diagnostic errors because of confounding clinical and radiographic features.

Clinical manifestations in the initial infection vary according to the age and immune response of the child. In general, the findings in children with relatively preserved immune function may be indistinguishable from that in non-HIV infected children, although the disease tends to be more severe, extrapulmonary (Fig. 2.1.2), drug resistant, and associated with atypical mycobacteria. The common presenting symptoms of



Fig. 2.1.2: Extrapulmonary TB caseating lymphadenopathy

primary pulmonary TB are cough, fever, anorexia, failure to gain weight, and fatigue. However, children may be asymptomatic despite abnormal radiographic findings. Physical findings may be relatively mild compared to the extent of radiographic findings and may include rales, rhonchi, bronchial breath sounds, and decreased breath sounds. In primary TB (Fig. 2.1.3) occurring as a result of recent infection, the process is generally seen as middle or lower lung zone infiltration, often associated with ipsilateral hilar adenopathy. In older children and adolescents, the disease presents as it does in adults with pleural effusion (Fig. 2.1.4) and cavitation (Fig. 2.1.5) with sputum smear positivity. Like adults, such patients present with fever, weight loss, a productive cough, hemoptysis, and night sweats. Radiographic findings include cavitary lesions typically situated in the upper lobes. Pediatric patients with TB are usually not infectious as they lack cavitary lesions with a large number of bacilli, and their relatively weak cough does not facilitate transmission of organisms. Although TB can occur in HIV/AIDS with any level of CD4+ counts, generally coinfected patients tend to have lower CD4+ counts. As HIV infection progresses and immunity declines, rapidly progressive disseminated disease is seen.

Multi-Drug Resistant-TB (MDR-TB), a rapidly emerging and potentially untreatable illness is defined as resistance to Isoniazid and Rifampicin with or without resistance to other drugs. In addition, Extensive Drug-Resistant (XDR) TB is defined as MDR-TB that is also resistant to any fluoroquinolone and one of the second line anti-TB injectable agents, i.e. kanamycin, amikacin, or capreomycin.

Refer to the chapter on HIV and Lung Manifestations for more details.

Central Nervous System

Infection with HIV can be complicated by involvement of the central nervous system (CNS). The CNS can be



Fig. 2.1.3: Primary complex of TB



Fig. 2.1.4: Left-sided pleural effusion with shift of mediastinum



Fig. 2.1.5: Bilateral fibrocavitatory TB

ffected either by HIV itself, opportunistic infections, eoplastic disease secondary to immune deficiency, or dverse effects of therapy.[10] CNS disease occurs more ommonly and at an earlier point in HIV infected children ompared to adults and is usually associated with gnificant immunodeficiency, increased viral load, and as a poor prognosis. To describe the emerging distinct inical and pathological pictures, the terms "HIV-1 ssociated progressive encephalopathy of childhood" (PE) r children and "AIDS Dementia Complex" (ADC) for dults have been proposed.[11]

Although similarities exist between PE and ADC, there re also important contrasting features (Table 2.1.5).

Table 2.1.5: Contrasting features of ADC in adults and PE in children

Adults	*Children*
lature CNS at primary infection	Immature CNS at primary infection
rain "atrophy"	Acquired microcepahy, impaired brain growth (Fig. 2.1.6)
'sychiatric changes common	Neurobehavioral changes common
lotor deterioration/cognitive lecline/dementia	Progressive motor dysfunction/ neurodevelopmental delay or regression
lo intracranial calcifications	Basal ganglionic calcifications (Fig. 2.1.7)
SF non-specific for ADC	CSF non-specific for PE
eizures frequent	Seizures infrequent
)pportunistic infections in CNS requent	Opportunistic infections in CNS infrequent

In HIV related encephalopathy (Fig. 2.1.8), there is lobal and severe deficit in cognitive, language, motor, and



Fig. 2.1.6: MRI of brain showing cerebral atrophy

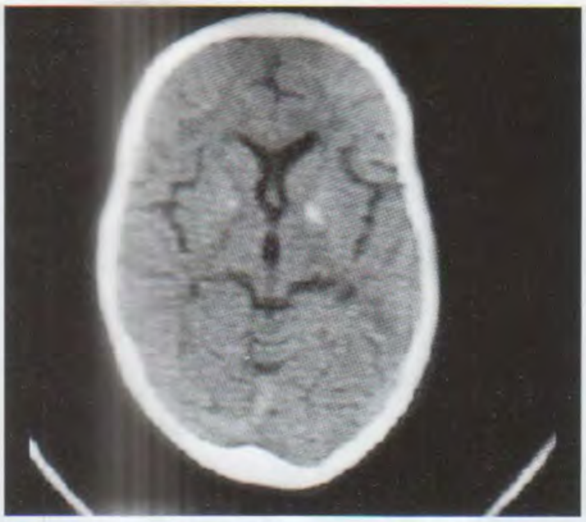


Fig. 2.1.7: CT of brain showing calcifications of basal ganglia

social skills, which may be either static or progressive Approximately 25 percent of CNS involvement manifest as a static encephalopathy usually presenting a developmental delay. In the progressive form there i neuroregression, behavioral abnormality, lack of socia responsiveness, apathy, microcephaly, spastic paresis anc hyperreflexia. Hepatosplenomegaly, lymphadenopathy and cardio-myopathy are also reported at higher rates ir children with encephalopathy.[12] The cause of HIV associated development delay is believed to be either a direct effect of HIV replication in glial astrocytes or AIDS related vasculitis.

Cerebrovascular complications occur in older childrer and present as focal neurological deficit, seizures headache, and abrupt changes in mental behavior. Stroke which is the most common presentation, may be due to



Fig. 2.1.8: HIV positive child with spastic encephalopathy

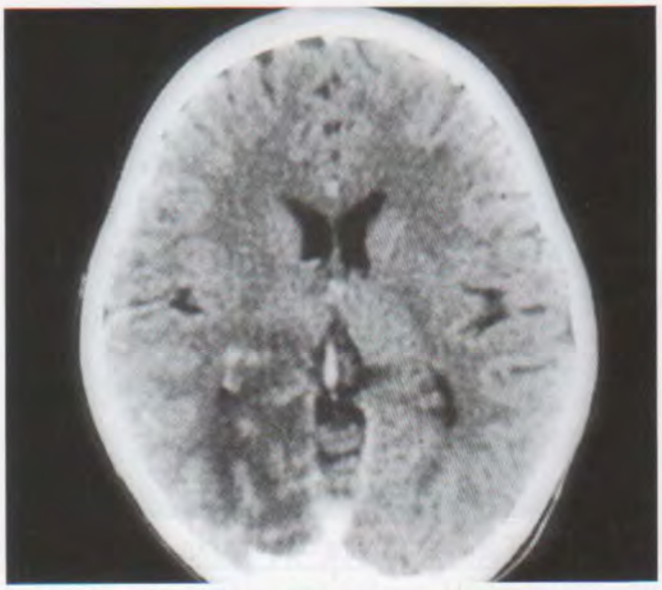


Fig. 2.1.9: Neuroimaging in a patient with stroke due to AIDS vasculopathy

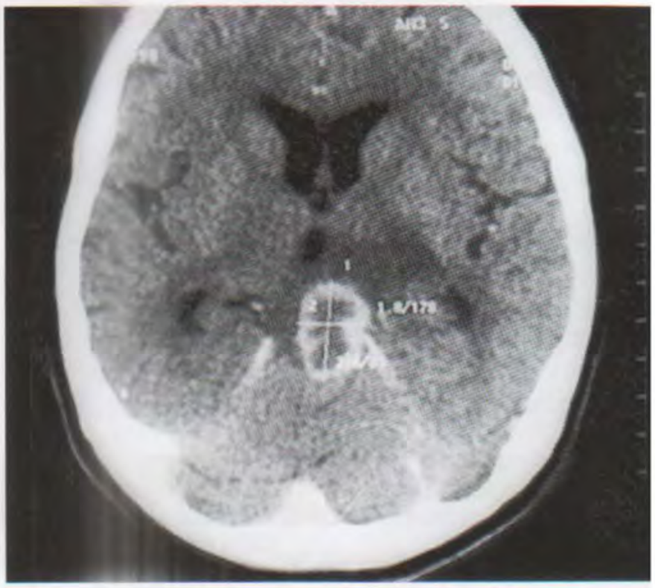


Fig. 2.1.10: CT brain, tuberculoma in posterior cranial fossa

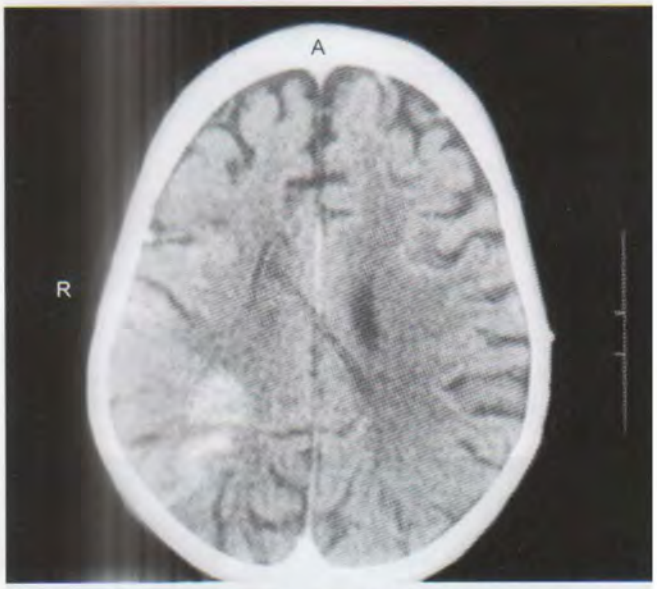


Fig. 2.1.11: Neuroimaging showing features of PML

ischemia or hemorrhage as a result of vasculitis or thrombocytopenia (Fig. 2.1.9).[2]

The most frequent opportunistic infections involving the CNS are tuberculosis, toxoplasmosis, cryptococcosis and cytomegalovirus. Although the incidence of these infections has decreased since the introduction of highly active antiretroviral therapy (HAART), they remain a major cause of morbidity and mortality. In practice, the diagnosis of these infections is often made by clinical presentation and non-invasive imaging studies, such as magnetic resonance imaging (MRI).

The HIV epidemic has been accompanied by a corresponding increase in the incidence of TB and HIV related TB cases. The problem of coinfection is further complicated due to drug interactions and low compliance. Tuberculous meningitis and tuberculomas (Fig. 2.1.10) often present with vague symptoms like headache, nausea, vomiting, fever and signs of meningeal irritation. Basal meningeal involvement often affects the cranial nerves, especially the oculomotor, trochlear, and abducens nerves.

Progressive Multifocal Leukoencephalopathy (PML) is a severe demyelinating disease of the CNS seen in immunocompromised patients. It is caused by JC virus (JCV), a group B human papovavirus. JCV reaches the CNS via leukocytes and then affects oligodendrocytes leading to extensive demyelination. It mainly affects the white matter but in some cases, the cerebellum and grey matter may be involved. The disease has an insidious onset and produces a neurologic syndrome that steadily progresses over weeks or months, characterized by confusion, disorientation, lack of energy, ataxia, cognitive dysfunction, dementia, seizures, aphasia, cranial nerve deficits, visual abnormalities (e.g. blurred vision, diplopia, or loss of vision), hemiparesis or quadraparesis, and eventually coma.

A confirmed diagnosis of PML requires a compatible clinical syndrome and radiographic findings coupled with brain biopsy. MRI has far greater sensitivity than other studies in detecting the lesions of PML and in defining the extent of involvement. Lesions are initially multiple and discrete, but eventually may coalesce into large lesions. They appear hyperintense on T2W images, and typically involve the periventricular and subcortical white matter. Lesions are more conspicuously visualized on fluid attenuated inversion recovery images (Fig. 2.1.11) appearing hyperintense against a background of

suppressed CSF signal intensity. On T1-weighted (T1W) images they appear hypointense and well demarcated, although they may be isointense in the initial phase of the disease. Although the disease may involve any part of the brain, it typically occurs in the parieto-occipital lobes and lesions appear to start in the subcortical white matter before extending to the periventricular white matter. Mass effect is infrequent and lesions are asymmetrical and do not enhance with contrast.

The diagnosis of PML is facilitated by use of PCR to detect JCV DNA in CSF, which may obviate the need for brain biopsy in patients with a compatible clinical syndrome and radiographic findings. JCV PCR positivity in CSF is highly sensitive (90-100%) and specific (92-100%) for PML. There is no specific treatment for PML and although a number of agents have been proposed, none have proven effective. The prognosis of PML is poor, with median interval between onset of the first symptoms and death being 3 to 6 months. However, with the use of ART the disease progression is slow, but complete remission is not the rule.[13] In fact, initiation of HAART can cause paradoxical worsening of PML as an immune reconstitution syndrome referred to as PML IRIS.

Cerebral Toxoplasmosis occurs in HIV patients with severe immunosuppression. It results from reactivation of a latent infection with *Toxoplasma gondii*, an intracellular parasite that affects birds, mammals and humans and is potentially life threatening. CNS Toxoplasmosis manifests as headache, change in cognitive status, seizures, fever, focal neurological deficit, including hemiparesis, ataxia and cranial nerve palsies. Diagnosis is usually made by the presence of specific immune antibodies and characteristic findings on imaging studies, which reveal multiple ring-enhancing lesions located in frontal, basal ganglia or parietal regions with surrounding edema and mass effect. CSF changes are nonspecific, ranging from normal to mild pleocytosis with protein elevation. The response to antitoxoplasma therapy, which is usually observed within the first 2 weeks, is also used for diagnostic purposes.

Cryptococcosis is a rare AIDS defining illness caused by the yeast *Cryptococcus neoformans*, and encephalitis is its most common manifestation. Patients may complain of headache, fever, confusion, and gait disorder and may have raised intracranial pressure although meningeal symptoms are usually absent. In the course of an immune reconstitution syndrome, clinical symptoms are often atypical and characterized by extensive abscesses. It can be diagnosed by identification of the organism in CSF by India ink staining or by detection of the cryptococcal capsular polysaccharide antigen. MRI findings may be nonspecific with isolated or multiple mass lesions which need to be differentiated from toxoplasmosis, lymphomas and tuberculomas. Effective treatment is available for both toxoplasmosis and cryptococcosis, although adverse effects are common and some patients may not respond to therapy.

Refer to the chapter on HIV and CNS Manifestations for more details.

Gastrointestinal and Hepatobiliary System

The gastrointestinal tract is a common site of opportunistic infections and neoplasms in HIV infected children. Factors predisposing to gastrointestinal involvement include decreased gastrointestinal immunity, decreased gastric secretion, diminished IgA response, and altered gastrointestinal motility.[2]

Infants and children with HIV commonly experience gastrointestinal problems, including oral and esophageal lesions, malabsorption, abdominal pain, dysphagia and acute or chronic diarrhoea. The most common oral condition is thrush, which is noted in those with low CD4+ T cell count. Oral candidiasis is associated with progression to AIDS, and persistent thrush should prompt a recommendation for HIV testing. Thrush commonly appears as cheesy white exudates (Fig. 2.1.12), as erythema without exudates, or as angular cheilitis. Similar lesions may also be seen in the setting of anemia or vitamin deficiency, however, those due to Candida typically respond to oral azole therapy. *Candida albicans*, CMV, and HSV are commonly responsible for dysphagia and odynophagia as a result of esophagitis and esophageal ulcers. Chronic bilateral enlargement of the parotid glands occurs in as many as 15 percent of children, and is due to direct infection of the parotid glands by HIV and lymphocytic infiltrates.

Diarrhea occurs frequently (Table 2.1.6) and may be acute, recurrent, or persistent. Persistent diarrhea is associated with severe immune suppression and growth impairment. There is a tenfold increase in the risk of death in HIV infected children due to diarrhea, and although enteric pathogens are responsible in the majority of cases



Fig. 2.1.12: Cheesy white exudates in a patient with oral thrush

Table 2.1.6: Etiology of diarrhea in HIV infected patients

Bacteria	*Salmonella, Shigella, Campylobacter, Yersinia enterocolitica, Escherichia coli, Clostridium difficile, Mycobacterium tuberculosis, Mycobacterium avium-intracellulare, Plesiomonas shigelloides, Aeromonas hydrophilia*
Virus	Cytomegalovirus, Adenovirus, Rotavirus, Norwalk virus, Calicivirus
Parasite	Entamoeba histolytica, Giardia lamblia, Cryptosporidium parvum, Isospora belli, Microsporidia
Fungus	*Candida albicans, Penicillium marneffei, Cryptococus neoformans, Histoplasma spp, Coccidoides immitis*
Neoplasm	Kaposi's sarcoma, lymphoma
Miscellaneous	Diffuse infiltrative lymphocytosis syndrome, HIV enteropathy, malabsorption, bacterial overgrowth, Zn deficiency

of diarrhea, the etiology may not be identified in upto one-third of the cases.

HIV enteropathy is a unique syndrome of chronic diarrhea in which causative agents cannot be detected. These patients have evidence of increased small bowel permeability, malabsorption of lipids and sugar, nonspecific histopathologic changes, and absence of pathogens. The exact pathogenesis of HIV enteropathy has yet to be clearly elucidated, however direct HIV mediated effect or cytokine-mediated mucosal changes have been postulated. Gastrointestinal infection by HIV causes dysregulation of the gut immunity leading to decreased IgA secretion and increased number of lymphocytes in the lamina propria, promoting bacterial overgrowth and production of endotoxins.[14]

Various etiologies contributing to hepatobiliary disorders in these patients have been reported, including infections, medications, and malignancies. Patients might present with jaundice, abdominal pain, nausea, vomiting, and abnormal liver function tests. Neither clinical features nor the liver function tests can reliably suggest the etiology, but infections due to *Mycobacterium avium intracellulare, Mycobacterium tuberculosis, Salmonella, Cryptoccoccus neoformans, Candida albicans, Histoplasma, CMV, HSV,* viral hepatitis, *Pneumocystis jirovecii, Cryptosporidium, Microsporidia* are common causes.

Viral hepatitis is more often diagnosed in HIV infected patients than in non-infected controls. Hepatitis B virus infection in these patients tends to become chronic and is associated with an increased risk of hepatitis D coinfection. In addition, the incidence of hepatitis C virus infection has risen. Infections with CMV or cryptococci mainly affect the biliary system and cause acalculous cholecystitis or secondary sclerosing cholangitis.

Apart from infections, malignancies and adverse effects of therapy can increase gastrointestinal and hepatobiliary manifestations. Since HIV infected patients require various medications, drug-induced hepatotoxicity should be strongly considered. Pancreatitis, which has a poor prognosis, is associated with *CMV, Cryptosporidium, Mycobacterium avium-intracellulare,* and *P. jiroveci* infection. The important risk factors attributed to pancreatitis are exposure to pentamidine isethionate and low CD4+ cell count.

Refer to the chapter on HIV and Hepatobiliary Manifestations for more details.

Cardiovascular System

Cardiac complications of HIV disease generally occur late in the progression of HIV/AIDS. They may be due to prolonged immunosuppression, opportunistic infections, viral infections, autoimmune response to viral infection, drug-related cardiotoxicity and nutritional deficiencies (Table 2.1.7).

Dilated cardiomyopathy as a result of HIV infection has a much worse prognosis compared to idiopathic dilated cardiomyopathy. Impaired myocardial growth and left ventricular dysfunction are thought to be immunologically mediated. Studies have failed to demonstrate any positive effect of HAART therapy on cardiomyopathy, although it may help to control CMV infections. An association between zidovudine and dilated cardiomyopathy has been reported in both adult and pediatric patients.[15]

Table 2.1.7: HIV associated cardiovascular abnormality

Type	*Possible etiologies and associations*
Dilated cardiomyopathy	HIV, Toxoplasma gondii, Coxsackie virus group B, Epstein-Barr virus, CMV, adenovirus, autoimmune response to infection, nucleoside analogs, IL-2, doxorubicin, interferons, nutritional deficiency/wasting, selenium, Vitamin B_{12}, carnitine, thyroid hormone, growth hormone, adrenal insufficiency; hyperinsulinemia TNF-α, nitric oxide, TGF-β, endothelin-1, Hypothermia/hyperthermia, autonomic insufficiency, encephalopathy
Coronary heart disease/arterial hypertension	Protease Inhibitor-induced metabolic and coagulative disorders, HIV induced endothelial dysfunction, Erythro erythropoietin-induced increase of hematocrit and blood viscosity
Pericardial effusion	*Staphylococcus, Streptococcus, Proteus, Nocardia, Pseudomonas, Klebsiella, Enterococcus, Listeria, Mycobacterium tuberculosis, M. avium-intracellulare, M. kansasii,* Herpes simplex virus, Herpes simplex virus type 2, cytomegalo virus, HIV, Cryptococcus, Toxoplasma, Histoplasma, Kaposi's sarcoma, Capillary leak, wasting, malnutrition, Hypothyroidism
Isolated right ventricular and pulmonary disease	Recurrent bronchopulmonary infections, pulmonary arteritis
Primary pulmonary hypertension	Pulmonary arteriopathy, mediator release from endothelium

Patients with HIV/AIDS are prone to coronary heart disease and hypertension, which may be caused by vasculitis as well as systemic metabolic changes. A wide range of inflammatory vasculitides such as polyarteritis nodosa, Henoch Schönlein purpura, and drug-induced hypersensitivity vasculitis occur in HIV infected individuals.[16] Vascular inflammation may result from HIV induced immunological abnormalities, stimulation of local monocytes and macrophages by the virus itself or other infectious agents. Amongst the ART medications, protease inhibitors lead to complications such as lipodystrophy, insulin resistance, and high levels of low density lipoprotein, cholesterol and triglycerides, which predispose to angina and myocardial infarction at a young age.

The incidence of pulmonary hypertension in HIV infected individuals is higher than in the general population. Common etiologies include lung infections, venous thromboembolism, and left ventricular dysfunction. Pulmonary hypertension detected on screening echocardiography or right heart catheterization warrants aggressive evaluation and treatment.

Pericardial effusion is another cardiac finding in HIV/AIDS patients. Its prevalence is estimated to be 22 percent.[17] It may be related to opportunistic infections or to malignancy (Kaposi's sarcoma, non-Hodgkin's lymphoma), but most often a clear etiology is not ascertained. Nevertheless, HIV infection should be included in the differential diagnosis of unexplained pericardial effusion or tamponade.

Involvement of the endocardium can cause serious complications like embolization of vegetations resulting in hematogenous spread of infection and infarction of distal tissues. The most frequent pathogens causing infective endocarditis are *Staphylococcus aureus, Candida albicans, Aspergillus fumigatus, Histoplasma capsulatum,* and *Cryptococcus neoformans*. Patients with and without HIV generally have a similar presentation, however, patients with late-stage HIV disease have higher mortality than do those in an earlier stage. Another pattern of involvement is nonbacterial thrombotic endocarditis (NBTE), in which an uninfected thrombus serves as a site of attachment for bacteria in the bloodstream.

Nutritional deficiencies are common in HIV infection, particularly in late-disease, and may contribute to ventricular dysfunction. Poor absorption from the gastrointestinal tract and chronic diarrhea lead to electrolyte and nutrient imbalances. Deficiencies of trace elements are associated with cardiomyopathy, and low levels of vitamin B_{12}, growth hormone, thyroid hormones and carnitine may cause ventricular dysfunction.

Refer to the chapter on HIV and Cardiovascular Manifestations.

Renal System

Renal impairment in patients with HIV infection may arise through a variety of different mechanisms. The majority of these are related to problems complicated by HIV associated immunodeficiency or the drugs used in treatment. The true prevalence of kidney disorders associated with HIV infection in African and Asian countries is unknown due to lack of surveillance and reporting of kidney disease in HIV positive patients, and also because in many pediatric centers renal biopsies are not performed regularly. Renal disease associated with HIV infection can be divided into four major groups: (1) acute tubular dysfunction with fluid and electrolyte abnormalities and/or renal failure caused by infections and nephrotoxic drugs, (2) HIV associated nephropathy (3) immune mediated glomerulopathies (IgA nephropathy, lupus-like syndromes, and (4) HIV associated thrombotic mesangiopathies, including atypical forms of haemolytic-uremic syndrome.

Table 2.1.8 shows the common cause of acute and chronic renal failure in patients with HIV infection.

Table 2.1.8: Common causes of renal failure in HIV

Acute renal failure	Drug related nephrotoxicity* Hemolytic-uremic syndrome Acute tubular necrosis (toxic/ischemic) Rhabdomyolysis, Intrarenal and extrarenal obstructive nephropathy (mostly drug induced)† HIV associated nephropathy Acute interstitial nephritis Membranoproliferative glomerulonephritis‡ Lupus-like glomerulonephritis IgA nephropathy
Chronic renal failure	HIV associated nephropathy Membranous glomerulonephritis Membranoproliferative glomerulonephritis IgA nephropathy

* For example, amphotericin B, foscarnet.
† Related to sulfonamides and indinavir.
‡ Usually related to hepatitis C or B.

In the era of HAART, the most common kidney disorder is the syndrome of HIV associated nephropathy (HIVAN), with a prevalence of approximately10-15 percent. HIVAN is characterized histologically by focal and segmental glomerulosclerosis with mesangiopathies, and clinically by acute or subacute progressive renal failure. Early features include proteinuria, urinary casts, fluid and electrolyte imbalances, and enlarged echogenic kidneys on ultrasound. Patients progressed rapidly to end-stage renal disease, with poor survival reported in the pre-HAART era. HIVAN usually develops in patients with severe immunosuppression and advanced disease. Survival is improved with early detection and use of HAART and ACE inhibitors. As the current cohort of

children survives to adulthood, the incidence of HIVAN is expected to increase; it is thus prudent that protocols for routine screening of proteinuria be implemented to ensure optimal outcomes.[18]

HIV associated nephrotic syndrome presents with heavy proteinuria, hypoalbuminuria, and normal or low cholesterol in contrast to the typical nephrotic syndrome of childhood. Peripheral edema is often mild or uncommon, probably due to the oncotic pressure being maintained by the hypergammaglobulinemia associated with HIV-1 infection.

Urinary tract infection (UTI) commonly due to *Escherichia coli* is a relatively common problem in these patients. UTIs in such patients have similar clinical presentations as the HIV free population, although there is a tendency for recurrence, infection with multiple organisms and resistant isolates, increasing the possibility of renal dysfunction.[19]

Children treated with indinavir have a high incidence of sterile leukocyturia and frequently their serum creatinine is increased to greater than 50 percent above normal. Tubulointerstitial nephritis, acute renal impairment and renal calculi are other complications associated with indinavir.

Refer to the chapter on HIV and Renal Manifestations.

Skin

Cutaneous manifestations are common in patients with HIV infection and tend to be more frequent as immunodeficiency progresses. Although most of the dermatological manifestations seen are disorders common in children in general, the immunocompromised child tends to have more severe, persistent, recurrent and resistant disease in spite of appropriate conventional therapy. They may also have unusual presentations. A variety of infectious, neoplastic and inflammatory conditions can produce cutaneous or oral lesions (Table 2.1.9).

A transient maculopapular rash may appear in the initial period that marks the stage of seroconversion. This is uncommonly seen in children as most of them are infected *in utero*. During the otherwise asymptomatic phase that follows, patients may develop seborrheic dermatitis, pruritic papular eruption and/or a variety of scaling dermatoses. Depression of cellular and humoral immunity can result in overwhelming infections like candidiasis, cellulitis, folliculitis, abscesses, varicella, molluscum and scabies. Many children with HIV infection have crusted or Norwegian scabies, in which the densities of mites are very high, and the appearance of the rash in these patients can be very misleading because of the diffuse papular or psoriasiform presentation.[20]

Table 2.1.9: Common HIV associated oral and cutaneous lesions

Lesions observed exclusively in HIV infection	Oral hairy leukoplakia Bacillary angiomatosis Kaposi's sarcoma
Lesions that occur with increased frequency or greater severity in HIV	Herpes simplex Varicella-zoster Molluscum contagiosum Staphylococcal infection Candidiasis Scabies Seborrheic dermatitis Psoriasis Atopic dermatitis Drug eruptions Aphthous ulcers Periodontal disease

The most frequent skin tumor associated with HIV disease is Kaposi's sarcoma (KS). In the 1980s, KS was amongst the most common AIDS illnesses, but since the introduction of ART, the prevalence has become relatively low. In contrast to classical KS that occurs in the elderly and affects only the skin of the lower extremities, HIV associated KS affects skin, mucus membrane, lymph nodes and internal organs such as stomach, lungs and liver. It manifests as a few asymptomatic purple macules or nodules with variable progression; the tumor can remain unchanged for months to years or it can grow rapidly with ulceration and hemorrhage.[21]

As in adults with AIDS, children with HIV infection are at an increased risk of developing drug eruptions, particularly to trimethoprim and sulfamethoxazole. Toxic epidermal necrolysis has been reported in infected children who receive antitubercular drugs or anticonvulsants.

Refer to the chapter on HIV and Skin Manifestations.

Hematological System

Hematological abnormalities are common in individuals with HIV infection. Impaired hematopoiesis, immune-mediated cytopenias, and altered coagulation mechanisms have all been described in HIV infected patients. These abnormalities may occur as a result of HIV infection itself, as sequelae of HIV related opportunistic infections and malignancies, or as a consequence of therapies employed in treatment.

Anemia occurs in up to 20-70 percent of HIV infected children. The most common causes include iron, folic acid and vitamin B_{12} deficiencies, immune hemolysis, drug toxicities, malignancy, and bone marrow suppression due to HIV and Parvovirus B-19 infection. Zidovudine (AZT)

therapy is probably the most common cause of anemia in HIV infected patients receiving ART. Marrow erythroid hypoplasia, aplasia, and megaloblastic maturation have developed as a result of AZT therapy. In combination with HIV infection, anemia may have an adverse effect on the quality of life.[22]

Thrombocytopenia is a common problem among HIV infected children. It may occur in the absence of other symptoms and, in some patients, is the initial manifestation. Possible etiologies of thrombocytopenia include immune-mediated platelet destruction, thrombotic thrombocytopenic purpura, impaired hematopoiesis, and toxic effects of medications. In some patients, however, thrombocytopenia is the only hematologic abnormality, and is associated with a normal or increased number of megakaryocytes in the bone marrow and elevated levels of platelet-associated immunoglobulin.[23]

The pathogenesis of granulocytopenia in patients with HIV infection is multifactorial. An autoimmune mechanism involving antigranulocyte antibodies and impaired granulopoiesis has been postulated, but not yet proved. Any infiltrative process involving the bone marrow due to infection, malignancy, or drug toxicity may also produce granulocytopenia.

Refer the chapter on HIV and Hematological Manifestations.

Growth, Nutrition and the Endocrine System

HIV infection diminishes growth in children. The two most common patterns affect different age groups. In early infancy, an apparent growth delay with symmetrical decrease in height and weight occurs, while in late childhood, as the disease progresses, there is a relative loss of weight for height. Pubertal delay, especially among boys, is common, and may contribute to the overall growth failure associated with HIV infection. The causes of growth dysregulation are varied, and can be due to alterations in gastrointestinal function, chronic or repetitive infections, and alterations in metabolic functions. Other possible explanations include a dysregulation of the hypothalamic-pituitary axis. The metabolic and endocrine effects may be the consequence of the primary infection or secondary to the use of medications. The viral burden is inversely related to the linear growth and body mass index. The use of antiviral medications that reduce viral burden is therefore associated with improvements in anthropometric indices of growth.[24]

HIV associated lipodystrophy is a syndrome that occurs in individuals with HIV infection who are being treated with antiretroviral medications. It is a progressive disease and its severity is directly proportional to age, duration of disease, and length of treatment. Lipohypertrophy is characterized by the presence of an enlarged dorsocervical fat pad, circumferential expansion of the neck, breast enlargement, and abdominal visceral fat accumulation. Lipoatrophy, in contrast, is characterized by peripheral fat wasting with loss of subcutaneous tissue in the face, arms, legs, and buttocks. Involvement of the face is the most common and carries a social stigma that may negatively affect the quality of life of patients with HIV. Other features include hyperlipidemia, insulin resistance, hyperinsulinemia, and hyperglycemia. Patients with HIV lipodystrophy syndrome are at increased risk for the development of atherosclerosis and diabetes mellitus.[25]

The term "Slim disease" (Fig. 2.1.13) was coined in the 1980s to describe an unexplainable but fatal condition of severe malnutrition affecting people in Uganda.[26]

This was later discovered to be due to HIV, and it underscores the importance of wasting amongst the many clinical manifestations of AIDS. The CDC defines wasting in children younger than 13 years as: (1) Persistent weight loss of more than 10 percent of the baseline; (2) Downward crossing of at least 2 percentile lines on the weight-for-age chart in a child 1 year or older; or (3) Being at less than the 5th percentile on weight-for-height or body mass index charts on 2 consecutive measurements at least 30 days apart, plus chronic diarrhea or documented fever for at least 30 days.

Protein-energy malnutrition is known to have adverse effects on the immune system, and coupled with HIV infection, the immunosuppression is therefore exacerbated.[27] High HIV viral loads, lower CD4+ cell counts, infections, and the use of nonprotease inhibitors are associated with an increased risk of growth failure. Children may present with a range of abnormal growth patterns such as symmetric delays in weight and height or severe wasting with normal height, and they tend to remain



Fig. 2.1.13: Severe wasting in AIDS (Slim disease)

below the standards for their age and gender even in subsequent follow-ups.

Malnutrition in HIV/AIDS has a multifactorial etiology and may be due to decreased intake, malabsorption, increased requirements, and psychosocial factors. Complications like peptic disease, opportunistic GIT infections, aphthous ulcers, pancreatic and biliary tract disease, or simply anorexia due to medications, all lead to a decreased intake of food. Malabsorption results from mucosal damage from local infections by HIV itself or other microorganisms, disaccharidase deficiency and protein-losing enteropathy. Sclerosing cholangitis, chronic pancreatitis, and hepatitis B and C also contribute to malabsorption. Systemic infections, fever, release of cytokines, neoplasms, and HAART medications are associated with increased tissue catabolism and hypermetabolism, and this consequently increases the nutritional requirements of the affected child. Finally, psychosocial factors like poverty, limited access to health care, and illness in other family members adversely affect nutrition in HIV infected children as well as in uninfected children.

Acknowledging the importance of wasting and growth failure in pediatric HIV/AIDS, certain guidelines have been recommended to ensure optimal nutritional care. Nutrition should be assessed in all patients regardless of symptoms. Counselling and education can guide patients to maintain an adequate diet, and the intake of vitamins and minerals should be 1-5 times the recommended dietary allowance. Specific nutritional support in the form of oral supplements or enteral tube feedings may be required, and parenteral administration is reserved for children with more threatening complications like severe malabsorption. Appetite stimulants and growth hormone can be considered in some patients. Drug nutrient interactions and side effects should be avoided and the metabolic complications of HAART should be monitored and evaluated. To aid in the implementation of these guidelines, a nutritional support team including a physician, nurse-specialist, nutritionist, and a social worker should be formed and consulted.

In conclusion, the multifactorial etiology of nutritional problems presents a complex problem in management of HIV/AIDS patients. While the incidence of malnutrition in industrialized countries is decreasing with the advent of HAART therapy, many children still face the complications of gastrointestinal dysfunction and wasting worldwide. In addition, HAART medications offer their own gamut of adverse effects like increased protein catabolism and lipodystrophy that modify the growth pattern of children under treatment. Future advances in assessment and treatment will thus play an important role in changing the prevalence of growth and endocrine disorders in HIV infected children.

Refer to the chapters on HIV and Growth, Nutrition and Endocrine Manifestations.

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2.2

Dermatological Manifestations of HIV in Children

Anisa Mosam

Introduction

Diseases affecting the skin and oral mucosa affect approximately 9 out of 10 who are infected with HIV. The cutaneous manifestations may be the initial declaration of diagnosis of HIV, whilst the immunity is still relatively robust, e.g. herpes zoster. It may occur further down in the course of HIV infection as the immunity is beginning to decline as seborrheic eczema or later on as a manifestation of full blown AIDS and a marker of severe immunodeficiency which if untreated will be fatal, e.g. disseminated histoplasmosis.

As with other systems, the skin can manifest with a number of signs of immune deficiency and as the CD4 declines and patients suffer with more severe immune deficiency, multiple skin pathologies present concurrently. These may require longer periods of therapy and may relapse more frequently as compared to those uninfected with HIV.

Hence, a thorough working knowledge of the cutaneous manifestations of HIV/AIDS cannot be overemphasized for those working with HIV infected individuals. Skin disease, although not a common cause of mortality, is a significant cause of morbidity, hence timely recognition and appropriate therapy will significantly improve the quality of life of these patients. This is even more critical in resource-constrained environments, where patients have poor access to antiretroviral therapy and hence suffer the manifestations of immune deficiency for much longer periods of time.

Since, an exhaustive description of the possible skin conditions that occur in HIV is beyond the scope of this chapter, the objective is to familiarize the healthcare professional with the common, important conditions that will improve the diagnosis and treatment of those with skin disease.

Cutaneous manifestations of HIV/AIDS can be classified broadly as follows:

Infections and Infestations

This is the largest group of cutaneous manifestations of HIV. It comprises fungal, viral, bacterial and parasitic infestations (Table 2.2.1). The infections which occur in HIV infected individuals are usually those that are common in general population but are usually more severe, resistant to conventional therapy, relapse more frequently and may require recurrent courses of therapy, e.g. oral candidiasis. Some conditions are peculiar to immunosuppression, e.g. cutaneous cryptococcosis and their presence will necessitate further investigation.

Inflammatory Conditions

The commonest conditions in this group are the seborrheic eczemas, pruritus, xerosis and papular eruptions. These, although not associated with mortality are extremely debilitating to the individual and simple measures can significantly improve the quality of life of the individual.

Tumors

Kaposi's sarcoma, Hodgkin's and Non-Hodgkin's lymphomas can present on the skin and although can be diagnosed through characteristic clinical appearance, require a histopathologic diagnosis and referral to oncology and hematology respectively.

HAART-related

This category deals mainly with skin manifestations of antiretrovirals as well as the manifestations of immune reconstitution which are directly related to restoration of cell-mediated immunity in the background of infections.

Table 2.2.1: Common cutaneous manifestations of HIV/AIDS

	Etiological group	*Specific condition*
Infections	Fungal	Oral candidiasis Tinea capitis, corporis, cruris and unguium Cryptococcosis Histoplasmosis Sporotrichosis
	Bacterial	Impetigo Ecthyma Tuberculosis Atypical Mycobacteria Syphilis Bacillary angiomatosis
	Viral	Herpes labialis and genitalis, Herpes zoster Chickenpox Warts Molluscum contagiosum Oral hairy leucoplakia
	Parasitic	Scabies Crusted scabies
Inflammatory	Eczema	Seborrheic eczema Pruritus Xerosis
	Papular eruptions	Eosinophilic folliculitis Papular Pruritic Eruption of HIV
	Nutritional	Zinc deficiency
	Drug eruptions	Morbilliform rashes Erythema multiforme Stevens Johnson's syndrome Psoriasis
Tumors	HHV 8	Kaposi's sarcoma Non Hodgkin's lymphoma Hodgkin's lymphoma
HAART-related	Drug eruptions Immune reconstitution	Immune reconstitution

The following are some of the commonly encountered AIDS-defining skin conditions:

- Kaposi's sarcoma
- Herpes simplex ulcers for >1 month
- Cryptococcosis
- Histoplamosis
- Atypical mycobacterial infection.

Correlation of dermatoses with CD4 count

- CD4 > 500 cells/mm³
  Herpes Zoster
- CD4 200-400 cells/mm³
  Candidiasis
  Dermatophyte infection
  Oral hairy leukoplakia
  Varicella zoster infection
  Seborrheic eczema
- CD4 < 200 cells/mm³
  Herpes simplex inf >1 month
  Cytomegalovirus
  Atypical mycobacterial infection
  Systemic fungal infection
  Drug reactions
  Papular eruptions

Herpes Simplex (Fig. 2.2.1)

This is a common infection caused by Herpes Simplex Virus type 1 (HSV-1) which presents as painful grouped vesicles on an erythematous base. The primary infection is a gingivostomatitis and children fall ill, pyrexial and have ulcers involving the oral mucosae. Recurrent HSV-1 presents with blisters and erosions involving the oral and perioral areas as well as sites which tend to become macerated, e.g. flexures. When the immunity is still robust, blisters are contained and heal spontaneously, but as the immunity declines, lesions are more atypical, remain as persistent ulcers and can be resistant to antiviral therapy. Children with extensive seborrheic eczema are prone to developing superimposed HSV 1 infection and should be managed with acyclovir. HSV ulcers present for longer than a month, are AIDS-defining and larger ulcers may be resistant to acyclovir therapy, necessitating foscarnet. HSV type 2 (HSV 2) is a sexually transmitted infection presenting with lesions on the genitalia but can be transmitted to babies from an infected mother; they respond well to antiviral therapy. HSV infection can recur as a manifestation of immune reconstitution on antiretroviral therapy (ART).



Fig. 2.2.1: Chronic painful ulcers involving the flexures. Macerated areas are prone to herpes virus infection

Varicella Zoster (Figs 2.2.2 and 2.2.3)

Chickenpox is a common childhood infection due to the Varicella Zoster Virus (VZV) infection presenting with truncal papules, vesicles and necrotic lesions. In children with HIV, the lesions tend to be more profuse, ulcerated, necrotic and hyperkeratotic. There is also a tendency for greater systemic involvement as pneumonits, encephalitis and hepatitis. In addition to chickenpox, herpes zoster infection occurs more commonly and after shorter intervals following VZV infection. This is usually the classical painful vesicular eruption within a dermatome, but may extend beyond the dermatome or be disseminated. The lesions can be hemorrhagic, infected, necrotic and can ulcerate to leave severe scarring post zoster. Here too, there is always the possibility of systemic involvement, hence children with suspected VZV infection should be assessed for systemic involvement as this will warrant intravenous acyclovir therapy. Due to the morbidity associated with VZV infections and the fact that VZV is not associated with progression to AIDS, it is recommended that HIV infected children are immunized with the live attenuated virus.[1,2,3]



Fig. 2.2.2: Vesicles of varicella zoster on an erythematous base in a truncal distribution typical of chickenpox



Fig. 2.2.3: Vesicles in a dermatomal distribution in Shingles

Molluscum Contagiosum (Fig. 2.2.4)

Molluscum contagiosum due to the *molluscipox* virus is another common childhood viral infection which resolves spontaneously once exposed to the underlying immunity. Typical lesions are pearly umbilicated papules and nodules with a central core which expresses whitish cheesy material. However, in immunocompromised children, they tend to be larger, more profuse, persistent and resistant to therapy. They are also known to recur as a manifestation of immune reconstitution. Although, a recent review found no therapies to be convincingly effective[4] a variety of surgical/destructive and medical therapies have been found to be effective in case reports. These are: cautery, cryotherapy, trichloracetic acid, imiquimod, retinoids and salicylic and lactic acid preparations.[4-7] Children should be discouraged from scratching so as to avoid autoinoculation.



Fig. 2.2.4: Umbilicated papules with a central cheesy core in molluscum contagiosum

Verrucae (Figs 2.2.5 to 2.2.7)

Viral warts due to the human papilloma virus are common in children. The common warts present as verrucous papules and nodules, commonly on the hands and feet. However, in immunocompromised children, they tend to be larger, more persistent and present commonly as flat topped warts (verruca plana). These are asymptomatic greyish flat-topped papules which occur on the face and can extend to the trunk. Condyloma accuminata usually occurs on genital areas and can present as small hypertrophic lesions or giant "cauliflower" growths. HIV infected individuals are commonly coinfected with multiple types of HPV which are persistent.[8] Warts may be quite persistent despite ART and in fact may become more profuse as a manifestation of immune reconstitution.[9,10]



Fig. 2.2.5: Verrucous papules on the tips of fingers and flat topped warts on the dorsum of fingers

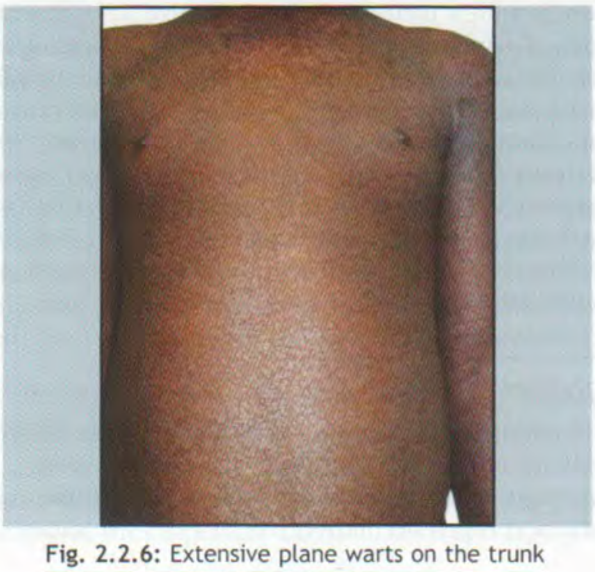


Fig. 2.2.6: Extensive plane warts on the trunk



Fig. 2.2.7: Verrucous cauliflower nodules in the groin in condyloma accuminata

Managing these children is quite challenging. Individual lesions can be treated with cryotherapy or cautery under local anaesthesia. However, more profuse lesions require other modalities, e.g. salicyclic preparations, imiquimod, retinoic acid, cantharidin and candida antigen. Imiquimod has been reported to be effective in facial warts, genital and extragenital warts.[11]

Scabies (Figs 2.2.8 and 2.2.9)

A common infestation in situations where overcrowding is rife caused by the parasite *sarcoptes scabiei*. The lesions present as they do in immunocompetent children with itchy papules, nodules and burrows involving the inner wrists and web spaces of the hands and feet as well as other warm protected areas like the axillae, groin, nipples and penis. However, as the CD4 declines, there is a tendency to develop crusted scabies where millions of mites are found in hyperkeratotic "psoriasisform plaques" involving the extensors, elbows, earlobes, nails in addition to the classic areas listed. Often, there is secondary bacterial infection and these patients may even be septicaemic due to the fissuring of the skin. Babies and young children may present with a vesicular eruption of the face and scalp.[12] The diagnosis can be confirmed by scraping and KOH preparation where the mites, ova or feces can be seen. In HIV repeated courses of therapy may be required. For children <2 years of age, 5 percent sulphur ointment is recommended as it is not as irritating and has antibacterial properties in addition. For children >2 years benzoyl benzoate is recommended applied over 3 days from the neck down to the toes with special attention given to the areas listed above. The drug of choice for crusted scabies is ivermectin 200 uk/kg, however, keratolytics are essential to debride the thickened plaques infested with scabies, e.g.



Fig. 2.2.8: Hyperkeratotic papules coalescing into plaques on the dorsa on the hands



Fig. 2.2.9: Truncal hyperkeratotic plaques accentuated in the axillae

5,10 and 20 percent salicylic acid or 5, 10 and 20 percent urea containing preparations.

Candidiasis (Fig. 2.2.10)

Although, candidiasis is the commonest mucocutaneous infection in HIV, in children <6 months is not a manifestation of immunosuppression. If it occurs beyond this period then there should be a heightened index of suspicion regarding underlying HIV infection. It presents as pseudomembranous (thrush), erythematous macules, hyperplastic (thick whitish-yellow plaques on the buccal mucosa) and angular cheilitis and is a reliable marker of progression of HIV infection. Children may also present



Fig. 2.2.10: Whitish cheesy plaques of candida on the dorsa of the tongue

with nail, nailfold and flexural involvement. Satellite erythematous papules at the periphery are clues to a candidial aetiology. In severely immunocompromised patients disseminated candidiasis can present as papules or pustules on an erythematous base and will require a smear or biopsy to make a diagnosis. Therapy with oral fluconazole is effective.

Superficial Fungal Infection (Fig. 2.2.11)

Dermatophyte infections caused by *Trichophyton, Epidermophyton and Microsporum* are common in children in the general community. They present as "ringworms" with scaly annular plaques with central clearing and advancing edges. However, in children with HIV, these lesions are extensive, atypical, resistant to therapy and there is a high incidence of nail involvement.[13] A high index of suspicion is required in any child presenting with pruritus and the diagnosis can be easily made by KOH preparation. Early recognition and systemic therapy are important in HIV infected patients to prevent severe infection. Griseofulvin is the first line antifungal therapy, however if patients do not respond then the azole antifungals or terbinafine are indicated at 5 mg/kg. Incompletely treated tinea infections can recur as a manifestation of immune reconstitution syndrome.

Pyoderma (Fig. 2.2.12)

The commonest causative organism for the above is *Staphylococcus aureus*. Although bacterial infections, i.e. impetigo, furuncles and ecthyma occur commonly in immunocompetent children, it is the extensive nature and



Fig. 2.2.11: Annular scaly plaques with an active erythematous border typical of tinea infection



Fig. 2.2.12: Folliculitis and furuncles due to staph infection

recurrence which occur in setting of immunosuppression. Folliculitis presents with painful papules and pustules, ecthyma with necrotic ulcers on the buttocks and lower limbs. Furuncles are fluctuant, painful, erythematous nodules. Bacterial folliculitis can recur as a manifestation of immune reconstitution. Localised lesions can be treated with topical antibiotics, but if more extensive lesions are present or the child has a fever then broad spectrum oral antibiotics would be appropriate. If the child is toxic, admission for intravenous antibiotics may be necessary.

Papular Urticaria (Fig. 2.2.13)

This is a common manifestation of HIV in children. They present with erythematous pruritic papules and nodules on exposed sites especially the face, arms and legs. The



Fig. 2.2.13: Truncal itchy papules secondary to insect bites

papules are usually grouped together/or linear, but may also occur on the trunk and other covered sites, e.g. buttocks. In HIV infected patients the response to insect bites is exaggerated, e.g. vesicular or bullous lesions.

Although it is difficult to differentiate between scabies and the papular eruptions of HIV since all are intensely pruritic, it is the distribution which differentiates these entities. Management is with topical steroid preparations and oral antihistamines.

Tuberculosis (Figs 2.2.14 and 2.2.15)

HIV infected children are more prone to developing tuberculosis and are more likely to present with cutaneous hypersensitivity reactions. This is a cell mediated immune response to underlying tuberculosis; pulmonary, lymph node, bone etc. Although, these are known to occur in immunocompetent patients, they have become more common and several types have co-existed in HIV infected children. A high index of suspicion should exist in any child with non-resolving lesions, more so in the setting of HIV.

- Lupus vulgaris presents as slow growing verrucous plaques which may be destructive. It mainly involves the face and ears
- Scrofuloderma presents as draining sinuses over-lying lymph nodes or bone.
- *Papulonecrotic tuberculid:* Papules, pustules which ulcerate and involve acral sites: ear lobes, elbows, knees, extensors and buttocks.
- *Lichen scrofulosorum:* Grouped papules on the trunk occurring with underlying lymphadenopathic and bone TB.
- *Erythema induratum:* Ulcers on the lower limbs with a bluish edge.



Fig. 2.2.14: Ulcerated plaque of lupus vulgaris involving central face



Fig. 2.2.15: Asymptomatic follicular papular eruption on the trunk with prominent cervical lymphadenopathy

Any of the above can coexists with each other. The diagnosis of any of the above tuberculids is supported by a strongly positive Mantoux, histology and a search for underlying TB. All the lesions of tuberculosis respond well to full antituberculous therapy for 6 months and if clinical response is not optimal, should be continued for 9 months.

Systemic Fungal Infections

Although, these are rarely seen in children, a high index of suspicion is warranted in children with severe immunosuppression. These conditions are AIDS-defining and present with ulcerated papules, nodules and ulcers which are non-specific. Clinicians should consider skin biopsy and culture early in ill children who are unresponsive to antibiotic and antituberculous therapy. In cryptococcosis skin lesions may be the first indication of underlying systemic fungal infection. The lesions are usually umbilicated haemorrhagic, ulcerated papules and nodules resembling molluscum contagiosum. Histoplasmosis is usually misdiagnosed as TB, as patients are usually ill with fever, anaemia, respiratory symptoms, lymphadenopathy, hepatosplenomegaly and skin lesions.

The skin lesions are nonspecific: Papules, nodules, plaques, abscesses but oral or nasal mucosal involvement is usually characteristic. Patients respond well to intravenous antifungal therapy if diagnosed and treated on time.

Seborrheic Eczema (Figs 2.2.16 and 2.2.17)

This is one of the commonest inflammatory dermatoses in HIV infected children. However, it is also a condition which occurs in healthy infants. However, it tends to be more severe and its onset more abrupt in HIV infected children. Although, one of the early manifestations of HIV, the eczema worsens as the CD4 declines. In babies lesions initially present with yellowish waxy plaques on the scalp and can extend to involve the face and flexures as well. On the face, there is erythema and scaling of the eyebrows and retroauricular areas which extends to the axillae, neck and groin folds. With uncontrolled disease, children often tend to become erythrodermic. Secondary bacterial infection is common as well as secondary herpesvirus infection. Children with darker skins often present with the tell tale post inflammatory hypopig-



Fig. 2.2.16: Erythema and postinflammatory hypopigmentation of central face in seborrheic eczema



Fig.2.2.17: Erythematous plaques in groin healing with hypopigmentation

mentation after the eczema has cleared. Therapy involves the use of topical steroid preparations and antihistamines.

Papular Eruptions of HIV (Fig. 2.2.18)

This entity refers to intensely pruritic papules which are commonly seen in HIV infected children. It can be a presenting sign of underlying HIV infection and usually is a sign of more advanced disease.[14, 15] The lesions are intensely itchy, folliculocentric, papules usually affecting the face, "V" of the neck and extensors of upper arms. It can extend to involve the trunk, upper and lower limbs. However, the web spaces, mucosae and palms and soles are spared, helping to differentiate it from scabies. [16] Since their aetiology is still under question, therapy is still symptomatic with topical steroids and antihistamines.



Fig. 2.2.18: Itchy erythematous papular eruption of the extensors

Children usually respond well to topical therapy and are not as distressed by the lesions as adults are.

Drug Eruptions (Figs 2.2.19 and 2.2.20)

Drug eruptions are a 100 times commoner in HIV compared to the general population and their prevalence increases as children progress from HIV to AIDS.[17,18] The most notorious are the group of antibiotics, responsible for atleast 75 percent of reactions. Trimethoprim sulfamethoxazole is the one responsible for most drug reactions followed by the penicillin-containing antibiotics. [18-20] Others often implicated are: anticonvulsants, antituberculous drugs and nonnucleoside reverse transcriptase inhibitors especially nevirapine. The pattern of drug eruption most commonly seen is the morbilliform; however, the commonest reaction pattern with nevirapine is urticaria/wheals. Targetoid or bulls-eye lesions, i.e central blisters and surrounding erythema should alert one to an underlying drug reaction. Stevens Johnson's syndrome is the involvement of atleast two mucosal surfaces whilst in Toxic epidermal necrolysis, there is stripping of at least 30 percent of the skin surface. The diagnosis of a drug eruption depends on the timing of the reaction in relation to the introduction of the drug. It occurs atleast 1 to 3 weeks after the initial exposure to a drug and 24 to 48 hours after reexposure. The morbilliform and urticarial lesions can be treated with antihistamines and if severe, oral steroids, provided there is no underlying hepatitis. However, if there is blistering, high fever and mucosal lesions, drugs should be stopped and these



Fig. 2.2.19: Morbilliform truncal eruption



Fig. 2.2.20: Extensive geographic hemorrhagic macules on the limbs

children referred for dermatological assessment as the morbidity and mortality is high.

Kaposi's Sarcoma (Figs 2.2.21 and 2.2.22)

This is the commonest cancer occurring in HIV/AIDS and in children usually presents with generalized lymphadenopathy. They rarely have the characteristic violaceous macules, plaques and tumours seen in adults. A high index of suspicion is required where children have unresolving lymphadenopathy, anaemia, rectal bleeding and pulmonary symptoms. Diagnosis requires biopsy for confirmation and referral for specific staging and therapy.



Fig. 2.2.21: Gross inguinal lymphadenopathy typical of childhood Kaposi's sarcoma. Overlying are extensive plane warts



Fig. 2.2.22: Erythematous nodules of Kaposi's sarcoma obstructing vision

HAART related

Class of Antiretroviral	Drugs	Side effects
NNRTI	Nevirapine and Efavirenz	Urticaria, morbilliform Erythema multiforme Steven Johnson's syndrome
NRTI	Zidovudine	Hyperpigmentation Vasculitis, paronychia
	Didanosine	Vasculitis, Steven Johnson's syndrome
	Lamivudine	Paronychia, pyogenic granuloma
	Zalcitabine	Oral ulcers, maculopapular rash, drug hypersensitivity
	Abacavir	Drug hypersensitivity
Protease inhibitors	Indinavir	Lipodystrophy, fissuring, xerosis, alopecia
	Ritonavir	Drug hypersensitivity
	Nelfinavir	Maculopapular eruption
	Saquinavir	Fixed drug eruption

Immune Reconstitution (Fig. 2.2.23)

Immune reconstitution inflammatory syndrome (IRIS) occurs as the worsening of underlying skin conditions after initiating ARV. It is related to reconstitution of the immunity with increased CD4 counts and decrease in the HIV viral loads and can be divided into unmasking or paradoxical IRIS. Previously treated infections or current infections can worsen or present for the first time during this period. Although, most infections can present as IRIS phenomena, the commonest are the viral infections, e.g. warts, herpesvirus infections and molluscum contagiosum. Hence, these conditions have to be treated independently of the underlying HIV.



Fig. 2.2.23: A verrucous papule of verruca vulgaris and umbilicated papule of molluscum contagiosum recurring on HAART

Conclusion

Although, the introduction of HAART has been associated with the dramatic decline in the prevalence of skin conditions associated with HIV/AIDS, the incidence of drug reactions has increased 100 fold and many infectious and noninfectious skin conditions recur as a manifestation of immune reconstitution. A thorough working knowledge of skin conditions affecting those infected with HIV is essential. This will empower healthcare professionals to improve the quality of life of patients with HIV/AIDS in both the developed and developing world.

Case Studies

Case 1

A case of an 8-year-old orphan living in a place of safety. He has been diagnosed with retroviral disease with a CD4 count of 160 cells/mm^3 and is awaiting HAART. He complains of an itchy eruption for the last month unresponsive to various topical therapies.



1. What are the possible differential diagnoses you will consider?
2. What methods can you employ to make a diagnosis?
3. How will you treat this patient?

Case 2

A 6-year-old HIV positive child on successful HAART for the last 3 years. His current CD4 count is 230 cells/mm^3 and HIV viral load is undetectable. His caregiver complains of the rash shown which is asymptomatic but very extensive and disfiguring, hence her concern.

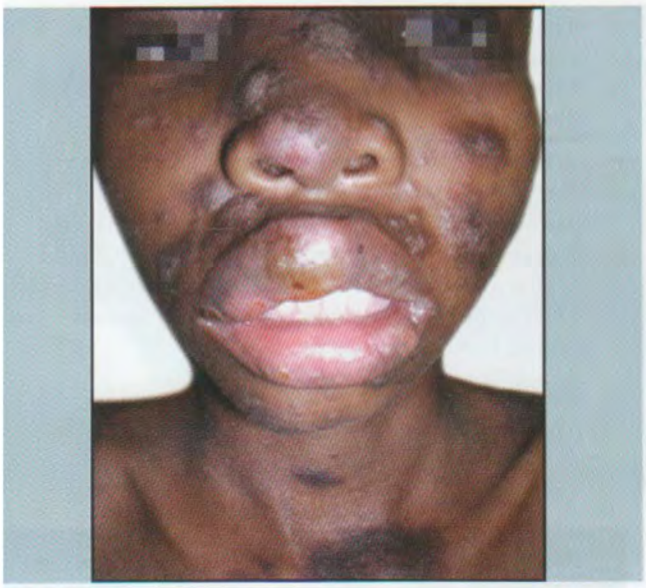
1. Describe the rash?
2. What are the possible differentials you will consider?
3. What is the cause of this rash?
4. How can you treat it?



Case 3

An 11-year-old child known to be HIV positive presents with an unresolving pyrexial illness, cough, loss of weight and rash of a months duration. She has been treated with antibiotics for an underlying pneumonia, but has not responded. She has been recently diagnosed with HIV and is not on HAART. Due to her status, the pneumonia and the pyrexial illness she is given antituberculous therapy, but still the pyrexia continues. She also has a pancytopaenia and a rash. The rash consists of scattered violaceous plaques and nodules with prominent upper lip swelling.

1. What are the possible differentials you will consider?
2. How will you investigate the patient above?
3. What are the conditions that can mimic tuberculosis?
4. A skin biopsy shows intracellular organisms which are PAS positive and *H. capsulatum* is cultured. How will you use the skin to stage the patient above?
5. How will you treat the patient above in the short term and with respect to long term prophylaxis?





Case 4

A 6-year-old child presents with an ulcerated plaque on the central face. He is otherwise well and his retroviral status is unknown. He has not responded to antibiotic therapy.

1. What are the possible causes of the lesion shown?
2. How will you investigate this patient?
3. What is your interpretation of the test in the picture below?
4. How will you treat this patient?



Answers

Case 1

1. Crusted Scabies; psoriasis, chronic eczema, extensive warts
2. KOH scrape and microscopy, biopsy
3. Keratolytics to debride the hyperkeratotic lesions (5-10 percent salicylic acid); Ascabiol (benzoyl benzoate) daily or Permethrin; Treat all contacts; wash linen, initiate HAART

Case 2

1. Hypopigmented flat-topped papules coalescing into plaques; widely distributed on the trunk and arms
2. Verruca plana; Epidermodysplasia verruciformis, warts
3. HPV
4. Topical salicylic acid-lactic acid preparations, 2-5 percent salicylic acid, topical tretinoin; topical imiquimod

Case 3

1. Disseminated furuncles; Kaposi's sarcoma; Systemic fungal infection, e.g. Histoplasmosis; Atypical mycobacterial infection
2. Skin biopsy and culture, bone marrow aspirate
3. PCP in the lung; Disseminated Kaposi's sarcoma; Atypical mycobacterial infection and Histoplasmosis
4. Disseminated fungal infection is AIDS defining; hence WHO stage 4
5. IVI Amphotericin B 1 mg/kg for 2 weeks; then Itraconazole 5 mg/kg daily until clearance and

mycological sure. HAART initiation and antifungal prophylaxis until the CD4 remains > 200 for 3 months.

Case 4

1. Cutaneous tuberculosis, chronic herpes virus infection; Deep fungal infection
2. Biopsy and culture, chest radiograph, mantoux
3. Ulcerated mantoux, i.e. highly positive grade 4
4. Initiate full antituberculous therapy.

Additional Recommended Reading

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2.3

Ocular Manifestations in Children with HIV

Rohan Chauhan, Deepa A Banker, Alay S Banker

Introduction

Pediatric cases of acquired immunodeficiency syndrome (AIDS) were first reported in 1982. Since then the number of cases reported each year has steadily increased and it represents 1.6 percent of all AIDS cases reported since 1981.[1] Pediatric and adult AIDS differ in mode of transmission of the virus, incubation period, and clinical course.[2] The incubation period in the pediatric group, although variable, can be quite short. Furthermore, a more rapid deterioration can be seen in pediatric AIDS. It is not known if the ocular findings in pediatric AIDS differ from those seen in the adult series reported by several authors. Very little information on the ocular findings in pediatric AIDS has appeared in the literature. Transmission of HIV from mother to infant is not absolute but is relatively efficient. Prospective studies have reported mother-to-infant HIV transmission in 13 to 39 percent of infants born to HIV infected women.[1]

Ocular manifestations can occur in up to 50 percent of AIDS children.[3] They can lead to severe visual loss affecting the quality of life of a HIV positive child. Common lesions include relatively benign conditions such as blepharitis and dry eye, to infections such as herpes zoster ophthalmicus and molluscum contagiosum and malignancies such as squamous cell carcinoma and Kaposi's sarcoma.[3] The posterior segment manifestations include retinal vasculopathy, opportunistic infections, unusual malignancies and neuro-ophthalmologic abnormalities; CMV retinitis being the commonest.[3] Effective antiretroviral therapy and improved prophylaxis and treatment of opportunistic infections have led to an increase in the survival of an individual afflicted with AIDS and decrease in the occurrence of these infections.[4] Immune recovery uveitis is a new cause of vision loss in children on HAART.[4] Diagnosis and treatment are guided by the particular conditions and immune status of the child. Kestelyn et al[5] reported a perivasculitis of the peripheral retinal vessels in 6 of 10 African children with AIDS-related complex.[5] However, in the same study, 8 children with full-blown AIDS had normal ocular examination results. Marion et al[6] reported "mild upward or downward obliquity of the eyes" and "long palpebral fissures with blue sclera" in their description of a possible craniofacial dysmorphism in 20 infants and children with AIDS.[6]

Ocular Manifestations of Pediatric HIV Infection

In spite of the widespread use of highly active antiretroviral therapy (HAART), today, ocular manifestations of AIDS at some point affect 50 to 75 percent of infected persons.[3] Opportunistic infections develop when there is a deterioration of the immune status of the individual which can be measured with the help of CD4 cell counts. Posterior segment lesions, especially cytomegalovirus (CMV) retinitis, can be associated with severe visual morbidity. Corneal and anterior segment lesions affect more than 50 percent of all HIV children.[3,7-9] Ocular adnexal complications, seen in about 25 percent of children, can be a sign of severe systemic immunosuppression. Also, the spectrum of ocular manifestations of AIDS in the developing world differs from that of developed nations.[3,7-9]

Opportunistic infections[3,9,10]

- **Retina**
  - CMV retinitis
    Complications—Immune recovery uveitis
  - Other retinal infections (caused by various agents, VZV, and *Toxoplasma gondii* being most common; most occur in less than 1 percent of children with AIDS).
- **Choroid** (uncommon; caused by various agents, fungi and mycobacteria being most common).
- **Ocular surface and adnexa** (important agents include VZV, microsporidia, Molluscum contagiosum virus).

Vascular abnormalities
- **Microvasculopathy**
  - HIV retinopathy (cotton-wool spots, retinal hemorrhages)
  - Retinal arteriolar and venular occlusions (uncommon)

Neoplasia
- Kaposi sarcoma (conjunctiva, eyelids)
- Lymphoma (intraocular)
- Squamous cell carcinoma (conjunctiva)

Other disorders of uncertain pathogenesis
- **Intraocular inflammation**
  - Chronic anterior uveitis (uncommon)
  - Chronic multifocal retinal infiltrates (uncommon)
  - Iatrogenic uveitis (drug related: cidofovir; rifabutin)
- **Blepharitis**
- **Dry eye**

Neuro-ophthalmic disorders associated with orbital or intracranial disease.

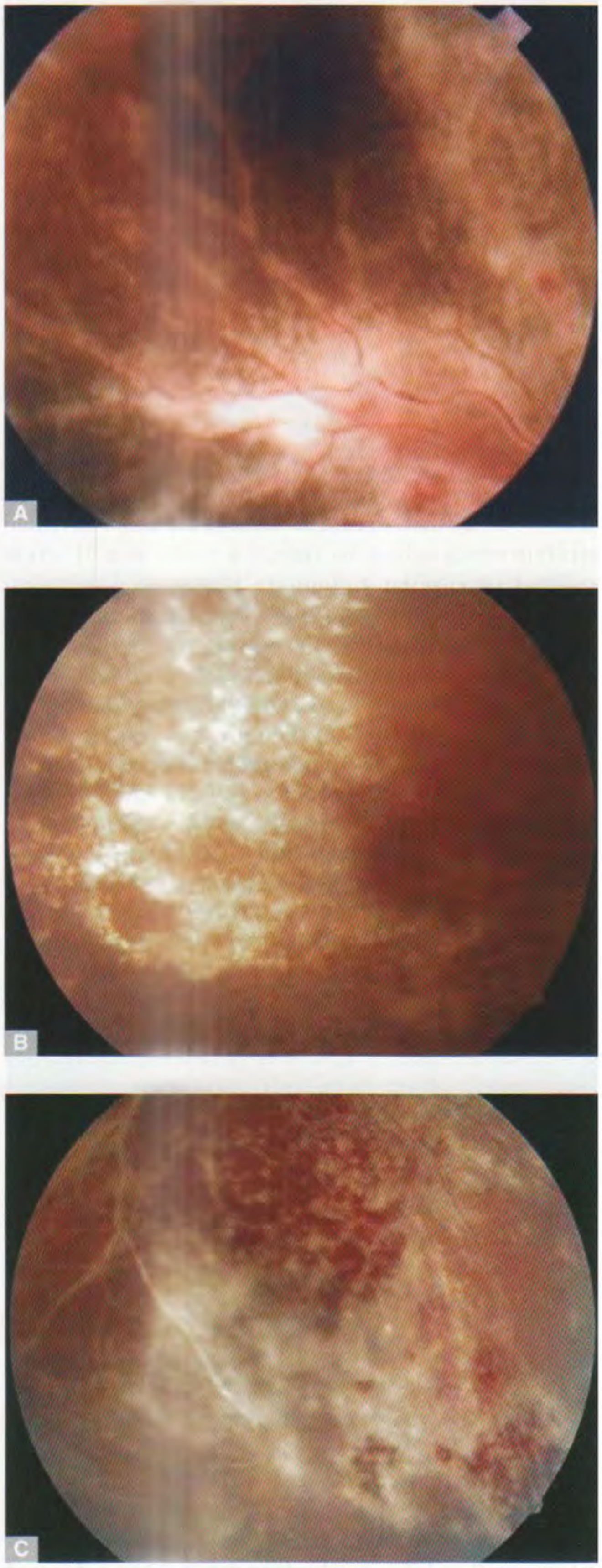
The spectrum of AIDS-related eye diseases differs in various parts of the world.[7] Squamous cell carcinoma of the conjunctiva and ocular tuberculosis have been greater problems in Africa than CMV retinitis, attributed to the fact that children die of other complications before reaching levels of immunodeficiency associated with CMV disease. During the early years of the epidemic in the United States, the prevalence of CMV retinitis increased as treatment of other life-threatening opportunistic infections improved, and children survived longer. As was feared, the same phenomenon is now being seen in the developing world. As treatments for HIV associated opportunistic infections and neoplasms improve worldwide, CMV retinitis may emerge as a global problem.[7,9]

Cytomegalovirus Retinitis (Figs 2.3.1A to C)

Cytomegalovirus retinitis is the most common AIDS-related ocular opportunistic infection and can develop in up to 40 to 50 percent of AIDS children prior to HAART.[9,11,12] Although its incidence has declined markedly since the advent of HAART in the western world, it still remains the leading cause of ocular morbidity in the developing countries.[9,11,12] In India, CMV retinitis still remains the commonest ocular manifestation in AIDS cases. In our series of 1286 cases, the incidence of CMV retinitis remains high even in the era of HAART. It may be unilateral to start with, but up to 52 percent will eventually develop bilateral disease.

Clinical Findings

There are three clinical forms of CMV retinitis.[12] The classical form (Pizza-pie retinopathy or cottage cheese with ketchup) is characterized by confluent retinal necrosis with



Figs 2.3.1 A to C: Active CMV retinitis

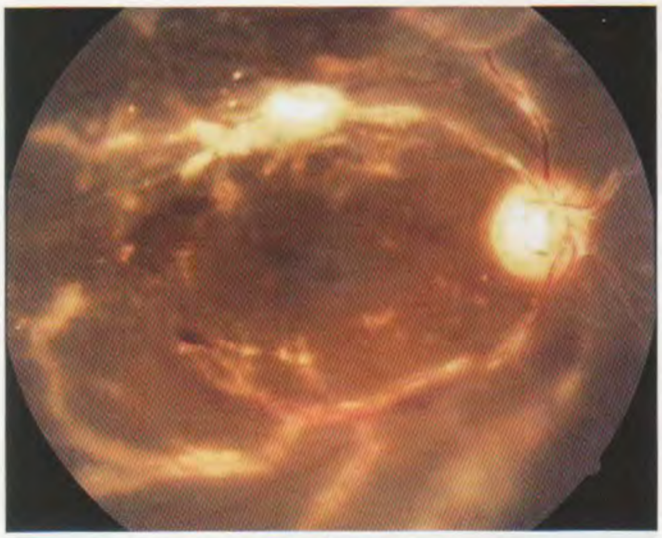
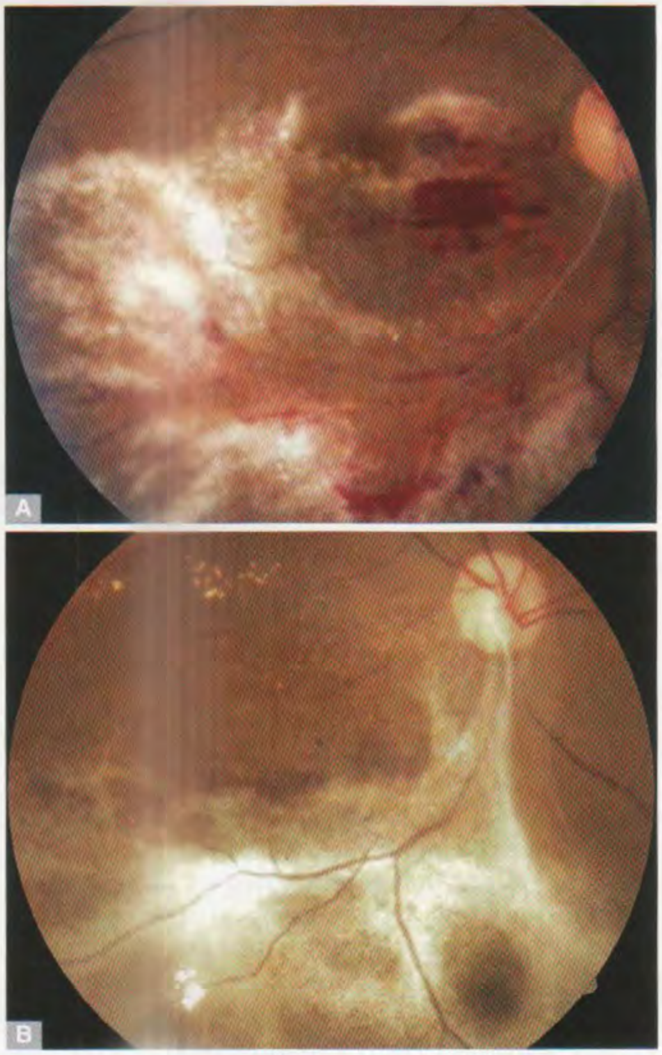


Fig. 2.3.2: Frosted branch angiitis



Figs 2.3.3A and B: (A) Pretreatment active CMV retinitis and (B) Healed CMV retinitis following intravitreal cidofovir

hemorrhage that develops mostly in the posterior retina. The advancing edge of these lesions is usually very sharp and spreads contiguously. In contrast, the indolent form is recognized as a granular lesion in the peripheral retina, often with little or no hemorrhage. A third uncommon presentation is frosted branch angiitis (Fig. 2.3.2).[12] Because approximately 15 percent of children with active CMV retinitis are asymptomatic, routine screening with dilated indirect ophthalmoscopy has been recommended at three-month intervals in children with CD4+ counts less than 50 cells/μl.[12] Cytomegalovirus retinitis may result in either serous or rhegmatogenous retinal detachment, although the latter is much more common. Rhegmatogenous retinal detachment has been reported in 13 to 29 percent of children with CMV retinitis and may occur during the active or healed phase of the disease.[9] However, since the advent of HAART, incidence of retinal detachment has decreased by approximately 60 to 77 percent in the western world. In contrast, in our series, the incidence of CMV-related retinal detachment was found to have increased. This may be due to higher number of children taking inappropriate HAART, or people taking HAART have larger areas of healed CMV retinitis which eventually develop necrotic holes leading to detachment.[9]

Treatment (Figs 2.3.3A and B)

Treatment of CMV retinitis is individualized and depends upon the location of the active retinitis and the immune status of the child. Currently available anti-CMV agents include ganciclovir and its prodrug valganciclovir, foscarnet, cidofovir, fomivirsen, ganciclovir implant and oral valganciclovir. We currently treat CMV retinitis by intravitreal cidofovir which is given in the dose of 15 microgram/0.1 ml.[9,12] When given along with HAART, most patients do not need repeated injections.[4,9,12] Treatment options are summarized in Table 2.3.1.

Initial Drug Treatment

The most important therapeutic maneuvre for the initial treatment of newly diagnosed CMV retinitis is to start HAART (for children not taking antiretroviral drugs) or to re-establish immune recovery (for HAART-failure children, by changing antiretroviral medications, if possible);[4,9] however, it is a common practice among HIV specialists to delay the start of HAART for children with systemic infectious diseases, such as tuberculosis, until treatments for the infections are started, to reduce the risk of systemic inflammatory reactions against the pathogens. The same may be true for reducing the risk of Immune Recovery uveitis (IRU).[9,12] After the start of HAART,

Table 2.3.1: Treatment for CMV retinitis

Medication	*Route*	*Induction dose*	*Maintainence dose*	*Adverse effects*
Ganciclovir	Intravenous for 2-3weeks	5 mg/kg bid for 2-3 weeks	5-10 mg/kg/day	Neutropenia, anemia, thrombocytopenia, liver toxicity
	Oral	–	1 gm tid	Same as intravenous ganciclovir
	Intravitreal	400-2000 µg twice/week	400-2000 µg once/week	Vitreous hemorrhage, retinal detachment, endophthalmitis
	Intraocular sustained-release Implant	4-6 mg pellet implanted through pars plana	Replaced every 6-8 months	Vitreous hemorrhage, retinal detachment, cataract, endophthalmitis, extraocular CMV, fellow-eye CMV, dislocated implants
Foscarnet	Intravenous	90 mg/kg bid for 2-3 weeks	90-120 mg/kg/day	Elevated creatinine, decreased Ca, Mg, K; Tetany
	Intravitreal	2400 µg twice/week	2400 µg once/week	Vitreous hemorrhage, retinal detachment
Cidofovir	Intravenous	5 mg/kg weekly for 2 weeks	5 mg/kg every other week	Proteinuria, renal failure, neutropenia, uveitis
	Intravitreal	15 ug/0.1ml	15 µg/0.1 ml every 6 weekly	Uveitis, ocular hypotony, Vitreous hemorrhage, retinal detachment, IRU
Valganciclovir	Oral	900 mg bid for 3 weeks	900 mg/d	Neutropenia,anemia, thrombocytopenia
Fomivirsen	Intravitreal	330 µg on days 1 and 15	330 µg monthly	Vitreous hemorrhage, retinal detachment, endophthalmitis, iritis

immune recovery is not achieved immediately; therefore, anti-CMV drugs should be given until certain immunologic (and possibly virologic) parameters are achieved. The induction treatment should be continued until CMV retinitis is inactive, to limit the size of lesions. Doing so presumably reduces the risk of retinal detachment and vision loss in individuals who have the prospect of prolonged survival.

Immune recovery allows eventual discontinuation of specific anti-CMV therapy without reactivation of infection. CMV retinitis eventually can reactivate after anti-CMV drugs are stopped; studies have estimated that the risk of recurrence is approximately 0.02 events/year.[12] Serial ophthalmic examinations and child education about symptoms of CMV retinitis are additional components of effective monitoring programs. Periodic screening examinations of children with CMV retinitis for reactivation (and of people at risk for new disease) is a well-accepted practice.

Necrotizing Herpetic Retinopathy[13,14]

Necrotizing Herpetic Retinopathy (NHR) is a continuous spectrum of posterior segment inflammation induced by herpes viruses, most commonly varicella zoster virus (VZV).[13,14] Its two most recognizable clinical patterns are acute retina necrosis (ARN) and progressive outer retinal necrosis (PORN). Usually, the former occurs in healthy persons and AIDS children with only mild immune dysfunction and elevated CD4+ counts, whereas the latter usually develops in those who are severely immunosuppressed.

Toxoplasmosis [8,9,13-16] (Fig. 2.3.4)

Ocular toxoplasmosis in AIDS, in contrast to toxoplasmosis in immunocompetent individuals, can be bilateral, multifocal, and not associated with chorioretinal scars. It may cause a variety of ocular abnormalities including iritis, vitritis, choroiditis, multifocal or diffuse necrotizing retinitis, papillitis or retrobulbar neuritis, or outer retinal toxoplasmosis.[15,16] Toxoplasma retinitis may resemble CMV retinitis; however, intraocular inflammation is usually more severe and hemorrhages are fewer.

Treatment

Treatment with standard antiparasitic drugs (Pyrimethamine, clindamycin, sulfonamides) is successful in controlling ocular toxoplasmosis in most cases.[15,16]

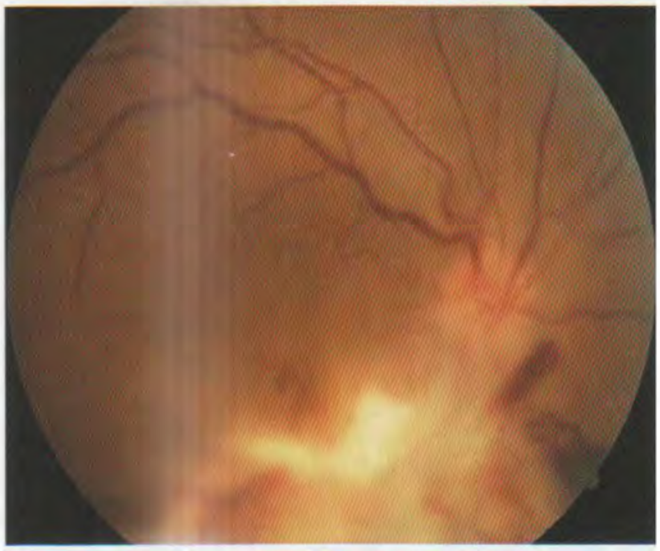


Fig. 2.3.4: CMV retinitis with toxo

Choroiditis

Pneumocystis

Ocular manifestations of *P. jerovecii* include conjunctivitis, orbital mass, optic neuropathy, and choroiditis. It is seen as classically bilateral and multifocal yellowish, well-demarcated, choroidal lesions located in the posterior pole not associated with vitritis, iritis, or vasculitis.[9] Ocular lesions respond in most cases to induction and subsequent maintenance treatment with systemic pentamidine, trimethoprim and sulfamethoxazole, or dapsone.[9]

Mycobacterial Disease (Fig. 2.3.5)

Mycobacterium tuberculosis is the commonest systemic opportunistic infection associated with AIDS even though ocular TB is not as common. It is important to consider it as a differential diagnosis, especially in developing countries like India.[8,9,11,13]

Clinical Manifestations

These include ulcers, tubercles, granular masses or pedunculated polypoid tumors. Children may present with localized nodule in the eyelid simulating chalazion. Orbital and lacrimal gland involvement by *M. tuberculosis* leads to localized granuloma though unusually they can present as a conjunctival mass.[8,9] Infection of the iris can present either with or without iris nodules. TB is also a known cause of uveitis, although it is uncommon, even among those with systemic TB. TB may cause interstitial keratitis with stromal infiltration. Interstitial keratitis secondary to TB may be associated with uveitis. It may occur as an isolated finding or in association with scleritis. Sclerokeratitis can be seen with peripheral stromal inflammation in a triangular fashion associated with localized scleritis. Localized lesions are focal elevated nodules of the sclera that may undergo necrosis leading to scleromalacia and scleral perforation if untreated. *M. tuberculosis* infection of the conjunctiva may involve the palpebral, bulbar, or forniceal conjunctiva. Tuberculous conjunctivitis is a very rare condition in the developed world. In recalcitrant cases of chronic red eye, a definitive diagnosis requires the identification of *Mycobacterium tuberculosis* organisms in conjunctival biopsy specimens, either through microscopic detection of acid-fast bacilli or through more sensitive culture techniques. Keratoconjunctivitis may occur in association with cutaneous TB. While intraocular disease is mostly a secondary infection, cutaneous TB is almost always primary. The commonest posterior segment manifestations include discrete choroidal tubercles or solitary mass like lesions of the posterior pole. Rarely, endogenous endophthalmitis also occurs.

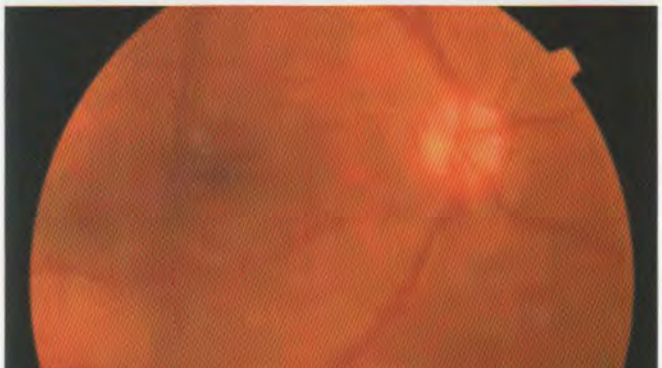


Fig. 2.3.5: Ocular tuberculosis

Treatment

Systemic Anti-Tuberculous Therapy (ATT) with drugs such as isoniazid, rifampin, pyrazinamide and ethambutol is important as pulmonary or other foci of disease may coexist. Modified DOTS regimen (Directly observed treatment short course) is the recommended regime in India. Specific ocular treatment should be instituted along with ATT.[8,9] There have been reports of scleral TB responding favorably to additional topical (every 2 hours) and subconjunctival (every three days) streptomycin sulfate along with ATT with healing of the lesion.

Fungal Infections

In the general population, fungal corneal ulcers are rare in the absence of preceding trauma, ocular surface disease or corticosteroid therapy while HIV/AIDS children can develop spontaneous fungal infections.[8,9,16] Candida causes anterior segment keratitis.[16] Cryptococci commonly triggers posterior segment pathology although they can sometimes cause conjunctivitis, limbal infection and iris granulomas.[16] *Cryptococcus albidus* causing scleral ulceration has been reported.[16] Histoplasma and pneumocystis are more likely to result in bilateral disease with corneal perforation.[16] Hence, culture or biopsy of lesions is important for HIV infected children with ocular surface infections, to differentiate between bacterial and fungal etiology.

Cryptococcus

Cryptococcal meningitis is the most common cause of AIDS-related neuro-ophthalmolgic lesions. Cryptococcal choroiditis may be multifocal, solitary, or confluent and may be associated with eyelid nodule, conjunctival mass, granulomatous iritis, iris mass, vitritis, necrotizing retinitis, endophthalmitis, and optic neuritis.

Treatment

Fluconazole maintenance therapy 200 mg/day is currently recommended in all children even in the era of HAART.[4]

Spirochetal Infections

Treponema Pallidum

Ocular syphilis caused by *Treponema pallidum* tends to present with more aggressive, severe and relapsing manifestations in HIV positive hosts as compared with immunocompetent hosts. All children with syphilis should be evaluated for HIV and vice versa. Anterior segment manifestations of syphilis include chancres of the conjunctiva (primary syphilis), conjunctivitis (secondary syphilis) and gummata (late syphilis). Conjunctivitis can be granulomatous and histologically similar to sarcoidosis.[16] The diagnosis of syphilis is done by serologic screening and confirmatory tests such as the rapid plasma reagin or fluorescent treponemal antibody absorbent tests, respectively. Direct examination using darkfield microscopy or biopsy of suspicious lesions can be performed if results are uncertain. Isolated episcleritis and scleritis are uncommon during any stage of the disease, but when present, are usually features of secondary or late *syphilis*.[8,9,16]

Treatment

It is similar to that of neurosyphilis. The most effective treatment involves high dose IV penicillin G 12 to 24 million units/day for 14 days. Because of the high rate of relapse, HIV positive children are recommended to have extensive follow-up subsequently at least for two years.

Bacterial Keratitis

The risk of infection with this "normal" flora may be greater for severely immunosuppressed individuals. *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Pseudomonas aeruginosa* are most frequently implicated.[8] Some cases of recalcitrant infection may require keratoplasty and even evisceration of the globe. Other risk factors predisposing to epithelial defects include the use of crack cocaine by HIV infected individuals.

Clinical Features

The clinical presentation of bacterial keratitis in HIV infected individuals differs from that in the general population. In immunosuppressed individuals, they are usually bilateral, involve multiple pathogens and carry a higher risk of perforation. There have been reports of eyes having to be eventually enucleated despite having been treated with intensive antibiotic therapy, based on *in vitro* sensitivities, for more than two weeks.[8] Paucity of inflammation in immunosuppressed children also contributes to delay in diagnosis and treatment. Gram staining and culture helps in the identification of the etiological agent.

Treatment

Systemic treatment with ceftriaxone or other appropriate antibiotics must be used to treat gonococcal conjunctivitis. Topical therapy alone will be ineffective.

Herpes Zoster Ophthalmicus (Fig.2.3.6)

Herpes Zoster Ophthalmicus (HZO) is caused by varicella zoster virus (VZV) which causes varicella (chicken pox) and herpes zoster (shingles).[13-16] Over 90 percent of the population develops clinical or serologic evidence of infection with VZV by adolescence, and the prevalence is almost 100 percent by age 60 years. The virus usually remains latent in sensory neurons. Herpes zoster eventually occurs in 10-20 percent of all individuals and reactivation in the ophthalmic division of the trigeminal nerve gives rise to HZO. Incidence of HZO is greater in HIV infected individuals than in noninfected, age-adjusted populations. Approximately 5-15 percent of HIV positive children are co-infected with herpes zoster, but only half of these individuals are at risk of ocular



Fig. 2.3.6: Herpes zoster ophthalmicus

involvement. It can even be an initial manifestation of HIV.[9] In immunosuppressed individuals, herpes zoster is more likely to be severe, prolonged, and can lead to viremia, which may result in visceral or neurologic infection, leading to increased morbidity and mortality. It is characterized by vesiculobullous rash over the distribution of the ophthalmic branch of the trigeminal nerve and may be associated with dendritiform and stromal keratitis, conjunctivitis, blepharitis, uveitis (with secondary glaucoma), hemorrhagic hypopyon, scleritis, retinitis or encephalitis.[9,13-16] Herpes zoster presenting in any apparently healthy young individual (<45 years) with these characteristics and without any obvious cause of immunosuppression should be investigated for HIV. Tissue damage can be mediated through a necrotizing vasculitis. Diagnosis of HZO is mainly clinical. To confirm a clinical diagnosis, however, various tests are available, including virus cultures, Tzanck smears, polymerase chain reaction (PCR) techniques for VZV/DNA, fluorescent antibody testing, and antigen detection by direct immunofluoresence.

Treatment

Treatment of HZO in individuals with HIV disease requires aggressive initial treatment, with intravenous acyclovir, followed by a prolonged course of oral antivirals as "maintenance therapy," to prevent recurrence. The regime is intravenous acyclovir (10 mg/kg of body weight eight-hourly for seven days followed by an oral maintenance regimen of 800 mg five times a day for at least three to six weeks).[9,13,14] Recently, oral valganciclovir has shown equal efficacy as intravenous acyclovir.

Molluscum Contagiosum[8]

Molluscum contagiosum, caused by a large DNA pox virus, affects up to 5 percent of HIV infected children and is highly contagious. It is transmitted by direct contact and has an incubation period of six to eight weeks. In immunocompetent children, it is transmitted via fomites, infected clothing, bedlinen, and towels. They are usually fewer in number, smaller in size and are found to be unilateral. In young adults, it is typically transmitted sexually. In HIV positive individuals, such lesions can occur in the eyelid and conjunctiva and are characteristically larger in number and size, often confluent, bilateral and resistant to therapy. Face, trunk and genitalia are commonly affected. A distribution in the chin-strap region is common in HIV positive children. The lash line should be examined carefully in all children with chronic conjunctivitis so as not to miss a molluscum lesion. It is characterized by pink or pearly white wart-like nodules on the skin. Sections of the lesions show large (20 to 30 microns) eosinophilic hyaline inclusion bodies which displace the nuclei to the margin. These bodies are composed of large numbers of virus particles, embedded in a protein matrix. Rarely, conjunctival involvement in AIDS children can also result in nodular pink lesions.[8]

Treatment

Typically, these lesions regress on their own in immunocompetent individuals. Treatment options include usage of topical agents like phenol and trichloroacetic acid or serial applications of liquid nitrogen. Incision with or without curettage, excision, and cryotherapy are equally effective.[8] Despite treatment, eyelid lesions will commonly recur. Administration of HAART with restoration of immunity leads to complete resolution of disseminated molluscum contagiosum and limitation of infection.

Vasculopathy[9,12]

Microvasculopathy is the most common ocular manifestation of AIDS, seen in about 40 to 60 percent of HIV positive children. Clinically, it manifests as cotton-wool spots located in the posterior pole and may simulate small patches of cytomegalovirus (CMV) retinitis.[9,12] However, unlike CMV retinitis, cotton-wool spots are not associated with large amounts of hemorrhages, subtle iritis, or mild posterior vitritis. They have more rounded borders, and are usually oriented along the vascular arcades, and represent focal areas of ischemia in the nerve fiber layer. Most children with retinal microvasculopathy are asymptomatic. Treatment is not indicated in most cases. The prevalence of microvasculopathy is inversely proportional to CD4+ count.[9,12]

Large Vessel Disease[9,12]

Large vessel occlusions, including central and branch retinal vein occlusions and branch retinal artery occlusions are uncommon and usually occur in association with viral retinitis, infiltrative lymphomatous optic neuropathy, and as isolated abnormalities. Usually visual prognosis is very poor once there is central vein occlusion. Frosted branch vasculitis has been associated with CMV retinitis in AIDS.[9,12]

Neoplasms

Squamous Cell Carcinoma of Conjunctiva[9,15,16]

SCC is one of the commonest neoplasms associated with HIV. The eyelid and conjunctiva is seldom a site of initial presentation in the developed world though they can be the first presenting sign of AIDS in up to 50 percent of

African children though it is not as common in the Indian population. The exact etiological role of HIV in ocular surface squamous cell neoplasia (OSSN) in Africa remains unclear.[3,8,9] Important cofactors in HIV associated OSSN may be UV-light induced DNA damage and HPV-infection. Sun-light related mutations of p53 a protein that has a crucial role in tumour suppression and cell-cycle control have been identified with high frequency in OSSN in HIV positive children. Most commonly noted clinical characteristics of conjunctival SCC are corneal overriding (90%), fast growth rates (with a rate of 1 mm in 83%), tumors larger than 1 cm (17%), changes in conjunctival color (66 %), and nasal locations (66 %).[3,8,9] When the tumor is found at the limbus, gonioscopy has to be performed to rule out intraocular extension.

Treatment

Wide excision with frozen section monitoring of the margins. Antiviral therapy from topical interferon as an alternative to radical surgery.[3,9]

Kaposi's Sarcoma of the Eyelid and the Conjunctiva[3,8,9]

Kaposi's sarcoma (KS) is a highly vascular mesenchymal tumor that appears as multiple purple-to-red nodules on the skin and mucous membranes. Kaposi's sarcoma of the eyelid and conjunctiva is rare in the Indian subcontinent possibly due to the rarity of the probable causative agent, human herpes virus.[8] The appearance of KS on the eyelids is similar to the lesions elsewhere on the skin. It can mimic a chalazion and can be seen in the upper or lower lids. Conjunctival lesions may be seen. Kaposi's sarcoma in the conjunctiva can be mistaken for a subconjunctival hemorrhage or pyogenic granuloma. Histologically, KS can resemble an angioma, hemangioma, lymphangioma or granulation tissue. It has a complex arrangement of capillary channels and vascular spaces (slits) without endothelium. Malignant spindle cells are arranged around these incomplete vascular spaces. The spindle-shaped interstitial cells are of vascular endothelial origin, with vacuolated cytoplasm which may demonstrate mitotic activity.[3,9]

Treatment

KS does not invade the eye and treatment is not necessary if it is asymptomatic and is cosmetically acceptable. The principal goal of therapy in this population is palliation when disease is disfiguring, painful, or interfering with function. It may be treated by cryotherapy, surgical excision (if the lesion is small), radiation and/or chemotherapy. Intralesional vinblastin or interferon alpha have known to produce good results.

Cutaneous and Conjunctival Lymphoma[3]

Non Hodgkin's lymphoma (NHL) accounts for 3.5-5 percent of AIDS-defining illnesses and tends to be of a higher grade of malignancy in HIV children and can affect eyelids and conjunctiva. Clinical abnormalities of the optic nerve in child with AIDS may be recognized as perineuritis, papilledema, papillitis, retrobulbar neuritis, and optic atrophy. NHL should be suspected in all HIV children of any age who have prominent vitreous cells, with or without subretinal exudation. Intraocular lymphoma usually is seen with CD4 cell counts of less than 50 cells/ml.[3]

Treatment

Radiotherapy and/or chemotherapy such as vinblastin. Interferon alpha has also been used as part of treatment modality.[3]

Other Manifestations

Keratoconjunctivitis Sicca (KCS)[3]

Dry eye occurs in 20-38.8 percent of HIV positive hosts in the later stages of AIDS. It is thought to be due to lymphocytic infiltration of the lacrimal gland. Etiology is multifactorial. Management options include artificial tears, long-acting lubricants and punctal occlusion in severe cases.[3]

Iatrogenic and Post-treatment Manifestations

Immune Recovery Uveitis[3,9,12]

The introduction of HAART brought with it the new ophthalmic problem of immune recovery uveitis (IRU),[3,4,9,12] which can be devastating for children whose health has otherwise improved, because it can result in vision loss. It is well accepted that IRU is caused by a response to CMV antigens, which is made possible by immune recovery. The reported incidence of IRU has varied from 0.1 to 0.8/per year of follow-up.[3,9,12] Risk factors for IRU include larger lesions and previous use of cidofovir, presumably because it also is associated with intraocular inflammation. IRU generally is recognized by the presence of complications of inflammation, including anterior chamber or vitreous reaction, panuveitis with hypopon, optic disk and cystoid macular edema, epiretinal membrane formation, cataract, vitreomacular traction syndrome, and proliferative vitreoretinopathy.[3,9,12] Treatment of IRU-associated macular edema has been difficult. Treatment with corticosteroids (subtenon or systemic or intravitreal) is effective in controlling inflammation and improving vision in some cases.[3,9,12]

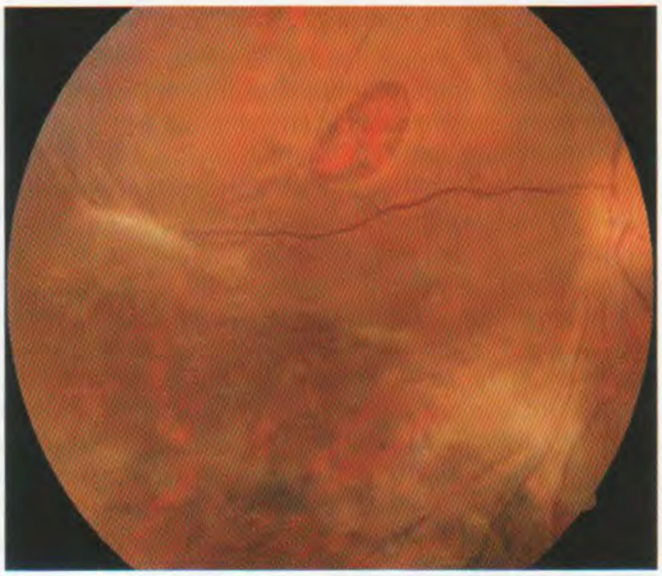


Fig. 2.3.7: CMV retinal detachment

Retinal Detachment (Fig. 2.3.7)

In the pre-HAART era, retinal detachments occurred in more than one-third of children with CMV retinitis who survived one year or longer.[3,9,12] Vitrectomy with silicone oil tamponade became the standard method for repair of these detachments. However, with the increasing longivity of these children due to use of HAART treatment, this may become an issue in the future. In the western countries, the risk of detachment is substantially less among children receiving HAART, which has been attributed to better control of infection, resulting in smaller, inactive lesions, and therefore better healed and more adherent scars.[3,12] However, in our series we found an increase in incidence of retinal detachment in children on HAART, may be due to a higher incidence of IRU and also larger areas of CMV retinitis which was untreated prior to starting the HAART.[3,9]

Drug-induced Uveitis[3]

Another group of new diseases has been attributed to the toxic effects of drugs, i.e. of Rifabutin and Cidofovir. In both instances, a predominantly anterior form of uveitis develops, which is characterized by a discrepancy between clinical symptoms and morphological changes; the former condition is distinguished by severe pain, and the latter by marked inflammation.[3]

Stevens-Johnson Syndrome (SJS)[3,9]

HIV infected individuals are frequently exposed to many medications, especially drugs such as nevirapine, which are capable of causing hypersensitivity or toxic reactions. Altered cell-mediated immunity may also lead to increased risk of SJS as a response to infectious agents as well. Associated dry eye may aggravate the problems associated with SJS in HIV infected individuals.[9]

Conclusion

Ocular opportunistic infections are becoming much less common in the era of HAART but they still remain as one of the commonest ocular complications of AIDS in the developing countries like India unlike the western world.[3,8,9,11] HAART has been shown to cause regression of CMV retinitis, increase time to relapse of CMV retinitis, reduce the incidence of CMV-related retinal detachments, and prolong child survival.[3] Anterior segment manifestations in the eye in HIV infected individuals are varied.[8] They can affect the quality of life which ultimately hampers the rehabilitation of the individual which is the ultimate goal. Multiple pathogens can be found in the same individual.[3] Children on HAART can develop severe inflammatory reaction due to immune recovery phenomenon which can cause severe ocular morbidity.[12]

Table 2.3.2: Treatment for other conditions

Necrotizing herpetic retinopathy	Intravenous acyclovir (10 mg/kg 8-hourly x 7 days followed by oral 800 mg five times a day for at least three to six weeks) oral Valganciclovir 1 G tid x 21 days
Toxoplasmosis	Pyrimethamine, clindamycin, sulphonamides
Pneumocystis	Systemic pentamidine, trimethoprim and sulfamethoxazole, or dapsone
Mycobacterial disease	Systemic antituberculous therapy (ATT)
Cryptococcal choroiditis	Fluconazole 200 mg/day
Ocular syphilis	Neurosyphilis high-dose IV penicillin G 12 to 24 million units/day for 14 days
Bacterial keratitis	Ceftriaxone
Herpes zoster ophthalmicus	Intravenous acyclovir (10 mg/kg 8-hourly x 7 days followed by oral 800 mg five times a day for at least three to six weeks) oral Valganciclovir 1 G tid x 21 days
Molluscum contagiosum	Phenol and trichloroacetic acid or liquid nitrogen. Incision with or without curettage, excision, and cryotherapy
Squamous cell carcinoma of conjunctiva	Wide excision with frozen section monitoring of the margins. Antiviral therapy from topical interferon

Contd...

Contd...

Kaposi's sarcoma	Rx is not necessary, cryotherapy, surgical excision (if the lesion is small), radiation and/or chemotherapy. Intralesional vinblastin or interferon alpha
Cutaneous and conjunctival lymphoma	Radiotherapy and/or chemotherapy such as vinblastin Interferon alpha
Keratoconjunctivitis sicca(KCS)	Artificial tears, long-acting lubricants and punctal occlusion
Immune recovery uveitis	Treatment with corticosteroids (subtenon or systemic or intravitreal)
Retinal detachment	Vitrectomy with silicone oil tamponade

Key Messages

- Ocular manifestations can occur in up to 50 percent of AIDS children
- Anterior segment lesions include blepharitis, dry eye, herpes zoster ophthalmicus and molluscum contagiosum
- Posterior segment manifestations are most commonly seen and include retinal vasculopathy, opportunistic infections, unusual malignancies and neuro-ophthalmologic abnormalities
- CMV retinitis is one of the commonest causes of severe vision loss
- HAART has been shown to cause regression of CMV retinitis, reduce the incidence of CMV-related retinal detachments, and prolong child survival.
- Immune recovery uveitis is a new cause of vision loss in children on HAART
- Diagnosis and treatment (Table 2.3.2) are guided by the particular conditions and immune status of the child.

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2.4

HIV/AIDS: A Pediatric Dentistry Perspective

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Introduction

HIV infection in children is a very sensitive topic. Often in our clinical practice we come across children infected with HIV. These innocent children have to face the wrath of the society and suffer the plight of the disease for no fault of their own. HIV infection erodes the immune system of these unfortunate children making them vulnerable to various infections.[1] Dental caries and periodontal disease are common bacterial infection of the oral cavity. Periodontal disease has been reported to be prevalent among HIV infected individuals. However, most of the studies reported have been conducted in adult populations.[2] Robinson et al reported a higher incidence of attachment loss, pocket depth, bleeding on probing and gingival changes in HIV + ve adults compared to HIV – ve controls.[3] Some longitudinal studies have reported the progression of periodontal disease in HIV + ve individuals to be faster compared to HIV – ve controls. Many reports have been based on subjects seeking dental care for their periodontal problems. In the vernacular of research, this is called as self-selection. It is evident that most studies carried out have been performed in adults with a fully developed immune system at the time of infection, but it is intriguing to know, how would the children born with HIV cope with the stress of a depleting immune system and an ever increasing burden of dental plaque?[4]

Apart from the morbidity occurring due to plaque-induced pathoses, the oral cavity also mirrors many signs during the early stages of HIV infection. Subtle mucosal changes of the oral cavity not only provide an opportunity to identify the individuals infected with HIV during the early stages of infection but can also be used as markers to assess the progress of the disease.

The oral manifestations associated with HIV infection are:

- Candidiasis
- Hairy leukoplakia
- Linear gingival erythema
- Periodontal diseases
- Dental caries
- Parotid gland enlargement
- Viral infections
- Kaposi's sarcoma

Classification of Oral Lesions

HIV infection depletes the immune system of an individual, hence these children are incapable of mounting an immunologic response, during the progression of infections. This is confounded by the fact that HIV infected individuals require medical intervention in the form of ART or repeated antibiotic regimens for systemic infections that suppress the periodontopathic microflora. However, one must understand that, with advances in medical science the study of HIV is not possible without the interference of treatment like antibiotics and ART. The role of HIV in the presentation of oral mucosal lesions is multifaceted. Although, the primary cause for development of oral lesions is attributed to the decreased immune response of the individual, the effect of antibiotics and antiretroviral drugs in the development of the oral manifestations present as an important confounding factor, specially in the presentation of bacterial infections.

The classification of oral lesions in children has been a matter of debate. The various classifications proposed have been based on the type of lesion, causative factors like bacterial, viral or fungal origin and frequency of occurrence of the lesion in the oral cavity. However, the 'Consensus Classification' proposed by Ramos-Gomez et al (1999)[5] provides easy to comprehend guidelines for early diagnosis of pediatric HIV infection.

The classification of oral lesions associated with HIV infection in children divides the oral manifestations in three categories (Box 2.4.1):

Group 1: Orofacial lesions commonly associated with pediatric HIV infection.
Group 2: Orofacial lesions less commonly associated with pediatric HIV infection.
Group 3: Orofacial lesions strongly associated with HIV infection but rare in children.

BoX 2.4.1: Classification of orofacial lesions associated with pediatric HIV infection consensus classification of orofacial lesions associated with pediatric HIV Infection Ramos-Gomez et al, 1999[5]

Group 1: Lesions commonly associated with pediatric HIV infection

- *Candidiasis*
  - Pseudomembranous
  - Erythematous
  - Angular cheilitis
- *Herpes simplex virus infection*
- *Linear gingival erythema*
- *Parotid enlargement*
- *Recurrent aphthous ulcers*
  - Minor
  - Major
  - Herpetiform

Group 2: Lesions less commonly associated with pediatric HIV infection

- *Bacterial infections of oral tissues*
  - Periodontal diseases
  - Necrotizing ulcerative gingivitis
  - Necrotizing ulcerative periodontitis
- *Necrotizing stomatitis*
- *Seborrheic dermatitis*
- *Viral infections*
  - Cytomegalovirus
  - Human papillomavirus
  - Molluscum contagiosum
  - Varicella zoster virus
  - Herpes zoster
- *Xerostomia*

Group 3: Lesions strongly associated with HIV infection but rare in children

- *Neoplasms*
  - Kaposi's sarcoma
  - Non-Hodgkin's lymphoma
- *Oral hairy leukoplakia*
- *Tuberculosis-related ulcers*

Oral Manifestation of HIV Infection

AIDS has emerged as a global crisis since its discovery in 1981 in the United States. The epicenter of the epidemic has now slowly, but surely shifted to Africa and Asia. By the end of 2004, around 42 million people in the world were infected with HIV/AIDS.[6] However, most of the studies pertaining to oral manifestations of HIV have been performed mainly in western countries[7-10] with Asian studies restricted mainly to Thailand.[11-13] Surprisingly, in India, only few studies have been reported so far.[14-17] There is a wide range of prevalence values for orofacial manifestations in the literature.[18-22] Possible explanations for this range are variable methodological factors, diagnostic criteria, examiner variability, and statistical analyzes.

Candidiasis has been documented in various studies as the most frequently occurring oral manifestation in HIV infected children, with a prevalence ranging from 20-72 percent.[23,24] Other lesions encountered include:

- Parotid enlargement
- Herpetic stomatitis
- Oral hairy leukoplakia
- Petechiae
- Aphthous stomatitis
- Linear gingival erythema
- Cervical lymphadenopathy

The occurrences of oral lesions that are recorded, also depend on the type of study design. The cross sectional prevalence studies and the longitudinal prevalence studies provide conflicting data regarding the true prevalence of oral mucosal lesions. This is suitably demonstrated in Table 2.4.1.

Table 2.4.1: Comparison of common oral lesions in longitudinal v/s cross-sectional studies (OC = Oral candidiasis, PC = Pseudomembranous candidiasis)

Author	Study duration	Common oral lesion
Howell et al (1996)	Cross sectional	OC (32%)
Katz et al (1993)	Longitudinal ± 3 years	OC (72%)
Ketchem et al (1993)	Cross sectional	OC (25.5%)
Moniaci et al (1993)	Longitudinal	PC (26%)

The important variables that determine the prevalence of oral mucosal lesions across different study designs include:

- Sample size
- Selection bias
- Inclusion criteria (e.g. patients under ART, mode of transmission, etc.)
- Diagnostic criteria
- Examiner variability

Orofacial Manifestations Associated with HIV Infection

Since the first descriptions of AIDS in 1981, the infection has been characterized as having significant oral manifestations in adult patients.[25,26] A number of oral lesions have also been associated with HIV seropositivity in children, but the incidence, progression and prognostic implications are not yet well understood.[27] Septicemia from an oral focus causes life threatening infection in the immunocompromised host. Consequently, careful evaluation of the oral tissues in children is an essential part of the pediatric dental examination. The types of oral lesions seen in HIV infection may be classified into fungal, viral, bacterial, neoplastic and idiopathic lesions.[28] The pediatric classification of orofacial lesions associated with HIV infection is divided into lesions which are commonly and rarely associated with HIV infection (Box 2.4.1).

GROUP 1: Orofacial Lesions Commonly Associated With Pediatric HIV Infection

Candidiasis

Recurrent candidiasis, which is persistent for long periods and often resistant to conventional antifungal therapy, is a frequent oral manifestation in pediatric HIV infection/AIDS.[29] Oral candidiasis (OC) is ranked as a Group 1 lesion in the classification of Oral lesions associated with HIV infection in children.[5] Oral thrush/candidiasis is also a finding in healthy infants in the first 6 months of life.[30] However, in the immunocompetent child, candidial lesions are often mild, readily amenable to treatment, or regress spontaneously and are rarely seen beyond infancy in the absence of predisposing factors. Candidiasis has been documented as the most frequently occurring oral manifestation in HIV infected children with a prevalence ranging from 20 to 76 percent. Among children who are HIV positive but symptom free, the prevalence of OC ranges from 11 to 20 percent, rising to over 70 percent in those with advanced HIV disease.[31] The median time to death has been reported as 3.4 years among children with oral candidiasis.[32] The prevalence of oropharyngeal candidiasis in seropositive patients who have not yet developed AIDS ranges from 7 to 48.[33] With progressive immunodeficiency (as reflected by a decrease in CD4 lymphocytes) the range increases from 43 to 93 percent.[34] Table 2.4.2 summarizes the prevalence of oral candidiasis in pediatric studies.

Table 2.4.2: Comparison of prevalence of oral candidiasis in pediatric studies

Author and Year	Sample	Country	Prevalence (%)
Ketchem et al (1990)	47	USA	25.5
Moniaci et al (1992)	69	Italy	35.5
Katz et al (1993)	99	USA	72.0
Chan et al (1994)	33	Canada	42.2
Valdez et al (1994)	NR*	NR*	35.0
Emodi et al (1998)	NR*	Nigeria	19.0
Chaloryoo et al (1998)	NR*	Thailand	59.6

NR* = Not Recorded

The mechanism by which the fungus converts from a commensal to a pathogenic form in response to HIV infection is unclear but the possibilities include:

- Increased adhesiveness and invasion
- Acquisition of virulent strains
- Phenotypic switching.[35]

It has been suggested that the presence of Candida can induce further immune suppression by toxic effects on lymphocytes. Xerostomia and low CD4 counts are factors that can lead to oral candidiasis.[36] Although the organism *Candida albicans* is primarily responsible for the infection, recent cytological and cultural studies have identified a different candidal organism associated with candidiasis in immune compromised patients viz. *C. dubliniensis*.[37]

The Consensus Classification for oral manifestations of pediatric HIV infection has included 3 variants of oral candidiasis. The clinical presentation of oral candidiasis in HIV infected children is variable. Chigurupati et al (1996)[38] described the clinical presentation of OC in HIV infected children as being diverse with manifestations of the pseudomembranous, erythematous and hyperplastic variants as well as angular cheilitis.[38] According to Ketchem et al (1990), the two most common types manifesting in children are the pseudomembranous and erythematous variants.[39] Pseudomembranous candidiasis

typically presents as white or yellowish plaques which, when scraped off, reveal a bleeding surface. These patches may occur on the tongue, buccal and labial mucosa, palate, and oropharynx. The mucosa may appear bright red where visible. The white plaques can be removed, revealing a bleeding surface. The color intensity may vary from fiery red patch to a hardly discernable pink spot. It is usually without clinical symptoms. When the tongue is affected, patchy depapillated areas appear[40] (Figs 2.4.1 to 2.4.3).

Erythematous or atrophic form appears as flat or raised red patches noted most often on the dorsum of the tongue, palate, and buccal mucosa. Angular cheilitis manifests as fissures or cracks at the commissures of the lips.[29] Once colonization and superficial infection by candida are established, deeper penetration into submucosal tissue may be facilitated by concomitant mucosal infections caused by HSV.[44] Chan et al[23] and Moniaci et al[42] found that there were more children with pseudomembranous candidiasis in stage P2 than stage P1 or P0 stages of HIV infection. Ketchem et al[39] noted in their cohort of HIV seropositive children, that most of the candidial lesions

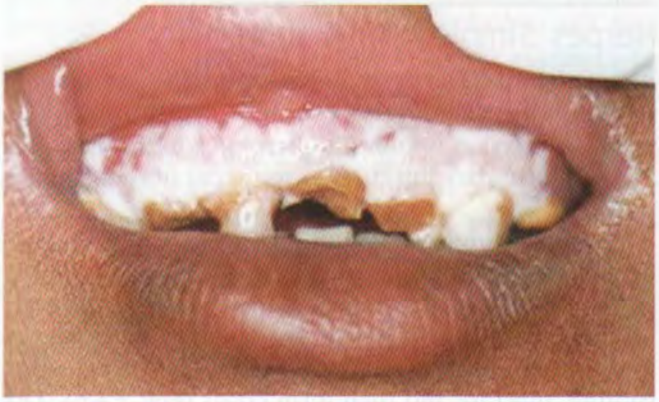


Fig. 2.4.1: Pseudomembranous candidiasis on maxillary anterior gingiva



Fig. 2.4.2: Pseudomembranous gingivitis of tongue



Fig. 2.4.3: Colonies of candida albicans on labial mucosa

were characteristic of the pseudomembranous type and affected large areas of the oral mucosa pseudotropicalis have been documented.[42]

In infants and small children, candidial lesions can be treated by swabbing with nystatin/gentian violet, or administering nystatin suspension (100,000 U/ml) in doses of 2 ml, three or four times a day. The suspension has no substantivity and is not well tolerated by infants, so that generally the solution is in contact with the oral mucosa for rather short periods of time. This may contribute in part to frequently reported unsuccessful treatment outcomes. The other disadvantage of the suspension is the high sucrose content.[40] In older children, the uses of nystatin pastilles (200,000 U/pastille), clotrimazole (10 rag/troche) troches are effective. Lesions may subside or disappear with treatment, but relapses are common due to underlying immunodeficiency. The antifungal therapy should continue for 1-2 weeks after clinical resolution of the symptoms. More severe cases require suppressive maintenance antifungal therapy and may be managed by ketaconazole 5-10 mg/kg/day or parenterally administered amphotericin B.[43]

Pseudomembranous Candidiasis

Presumptive Criteria[44]

Multifocal, non-adherent, creamy white papules or plaques that can be wiped off with minimal pressure leaving an erythematous surface. Pinpoint or petechial bleeding may be observed occasionally after removal of the superficial coating. In general, these lesions are widespread and may be located anywhere in the oropharyngeal area.

Definitive Criteria[44]

The patient's response to antifungal therapy is the principal defining criteria for tests for the presence of Candida spp. Culture/smear may be helpful, particularly

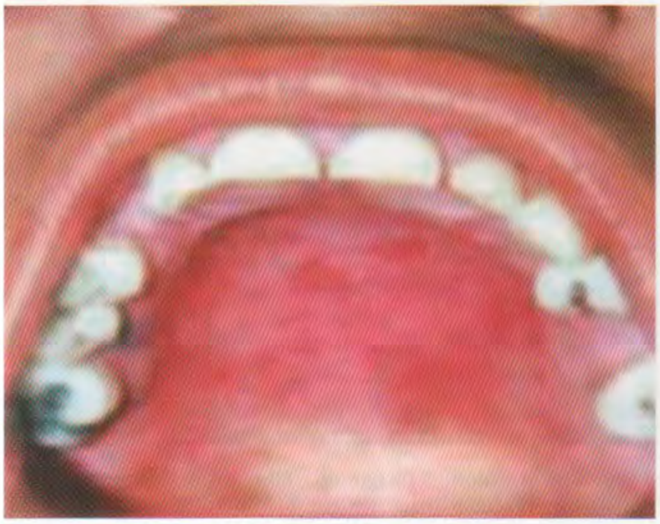


Fig. 2.4.4: Erythematous candidiasis

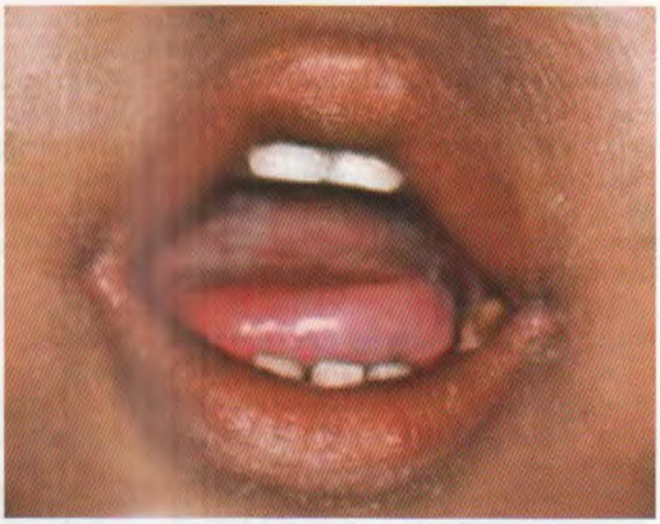


Fig. 2.4.5: Angular cheilitis

if the patient does not respond to antifungal treatment due to potential resistance.

Erythematous Candidiasis (Fig. 2.4.4)

Presumptive Criteria[44]

Multiple, flat red patches of varying intensity, most commonly located on the dorsum of the tongue. Non - adherent, filmy white-to-creamy plaques may be seen concurrently with this form of candidiasis. Median rhomboid glossitis, which is usually a red, smooth, depapillated patch on the mid-dorsal tongue is a variant of this form. Tenderness or a burning sensation may be experienced.

Definitive Criteria[44]

Definitive diagnosis may be assisted by detection of *Candida* spp. in culture or cytologic smear or by the patient's response to antifungal treatment.

Angular Cheilitis (Fig. 2.4.5)

Presumptive Criteria[44]

Linear red or ulcerated fissures radiating from the corners of the mouth. Typically, the lesions are bilateral, and multiple red papules may be found when the adjacent perioral skin is involved. Concurrent intraoral candidal involvement is a common clinical finding. These lesions are usually tender and slow to heal because of repeated irritation from opening the mouth.

Definitive Criteria[44]

Definitive diagnosis may be assisted by detection of intraoral *Candida* spp. in culture or cytologic smear or by the patient's response to antifungal therapies. A staphylococcal or streptococcal coinfection may be present in some cases.

Herpes Simplex Virus Infections

Infection by the Herpes Simplex Virus (HSV) causes both primary and secondary/recurrent oral lesions. The primary infection is known as herpetic gingivostomatitis and the secondary infection as recurrent herpes simplex infection.

Herpetic gingivostomatitis presents as multiple ulcers on the gingiva, buccal mucosa and tongue while the secondary or recurrent infection presents as a 'cold-sore' on the vermillion border of the lip, or vesicles on the intraoral mucosa. Lip lesions appear as small vesicles that rupture, ulcerate and then form crusts (Fig. 2.4.6). The intraoral lesions appear as small crops of vesicles on the hard palate or gingiva that rupture to produce small painful ulcers. The oral lesions are usually confined to the



Fig. 2.4.6: Herpes simplex virus infection

keratinized mucosa, although lesions may appear on the dorsal surface of the tongue. Primary HSV lesions also are seen in the healthy child between ages 2 to 6 years. However, in healthy children, HSV lesions resolve in 10 to 14 days and generally require only palliative treatment. Infection by the HSV virus is common in HIV negative children and young adults. Herpetic stomatitis caused by herpes simplex virus (HSV) is commonly seen in HIV infected children and has a tendency to recur (two or more episodes within a year).[45,40]

In HIV infected children these, lesions are chronic, recurrent, and may progress rapidly to cause extensive mucocutaneous involvement. As immunosuppression increases, an increase in severity and frequency of recurrences of orolabial lesions occurs. Recurrent HSV infection affects the lips and intraoral mucosa of approximately 10 to 25 percent of people with HIV infection. The reported prevalence for HSV infections in HIV infected children ranges from 1.7 to 24 percent.[5] Leggott (1992) states that Herpes SV-1 is commonly seen in HIV infected children and recurs more than twice a year. In HIV infected children, severe, chronic, painful, recurrent lesions may occur on all membranes and may require hospitalization. The lesions appear as crater-like ulcers with well-defined, raised borders and a gray pseudomembrane.[40]

Early diagnosis and treatment of lesions with antiviral agents such as acyclovir is important in HIV infected children with severe, long standing, painful lesions because they may prohibit oral intake. In a study by Katz et al HSV was manifested in 30 percent of the children within 5 years from the date of acquiring HIV infection. These lesions were not significantly related to survival time, unlike candidiasis and parotitis.[45] Diagnosis of oral HSV lesions is simple due to typical clinical presentation, but atypical lesions should be scraped and examined for intranuclear inclusions and multinucleated giant cells. Most herpetic lesions, even in HIV infected children are self-limiting. When lesions do persist however, they can be treated with systemic antiviral agents such as acyclovir. Oral acyclovir may be indicated for treatment of intra-oral lesions and herpes labialis. Foscarnet (trisodium phosphonoformate hexahydrate) has proven to be an effective treatment for resistant herpetic lesions in adults and children.[5] Other viral lesions manifested in the oral cavity include ulcers involving the tongue, palate, buccal mucosa, and pharynx caused by varicella zoster and coxsackie virus. These lesions also are seen in healthy children and are not specific to children with HIV infection.

Presumptive Criteria[44]

Patients will exhibit fever and malaise, swollen and tender lymph nodes, and intra and perioral lesions on the gingiva, hard palate, and vermillion border of the lips. However, any mucosal site may be involved. Initially present as vesicles, these lesions rupture to become painful, irregular ulcers.

Definitive Criteria[44]

Confirmation of a diagnosis of herpetic infection by laboratory methods is available but rarely used. The virus may be isolated in tissue culture. Intact intraoral vesicles are rare. Cytologic examination reveals ballooning degeneration of infected epithelial cells and nuclear inclusion bodies, but does not permit viral identification. Therefore, DNA hybridization is necessary for a definitive diagnosis.

NOTE: Although non-HIV infected children usually recover swiftly and completely from herpes simplex infection, HIV infected children frequently have severe intraoral lesions that may require hospitalization. Hospitalization is not routine for HSV infection in children. Moreover, the lesions tend to recur on the oral mucosa and on adjacent facial areas over prolonged periods. Recurrent cases are characterized by extensive lesions and marked crust formations on the vermillion border.

Gingival and Periodontal Lesions

Although, a study conducted by Sheutz et al (1997)[46] does not support the view that there is an association between periodontal conditions and HIV infection, the EC-Clearinghouse Classification and Consensus Classification (Box 2.4.1), classifies periodontal disease as conditions commonly associated with HIV infection.

Gingivitis and periodontitis can occur in both HIV positive and HIV negative individuals. There are, however, periodontal problems that are, unique to HIV infection. Linear Gingival Erythema (LGE) (Figs 2.4.7A and B) previously known as HIV gingivitis and Necrotising Ulcerative Periodontitis (NUP) (formerly known as HIV periodontitis) are two such conditions. Periodontal disease in HIV infected adults, although not clearly defined, has been well described in the literature. In a study by San Martin,[47] children were examined specifically for periodontal disease. The results of this study indicated that 37.3 percent presented with HIV G (LGE), 4.5 percent with HIV-P (NUP) and 58.2 percent with conventional gingivitis. This study suggests that HIV-G is strongly associated with HIV infection in children. Linear gingival erythema (LGE) and necrotizing ulcerative periodontitis (NUP) occur frequently in HIV infected adults[48] and have been reported occasionally in children with perinatally acquired HIV infection. Microbiologic studies revealed the prevalence of Actinobacillus *Actinomycetem comitans* and *Candida albicans* from the lesions of LGE and NUP.[49]

Linear gingival erythema (LGE) appears as a profound red (erythematous) band affecting the marginal gingiva along the necks of the teeth. It may vary in width and is

disproportionate to the amount of plaque present. It may also be described as a fiery red, linear band 2 -3mm wide on the marginal gingiva accompanied by petechiae-like or diffuse red lesions on the attached gingiva and oral mucosa. According to Greenspan et al (1996), this lesion was not recognized before the AIDS epidemic.[31]

However, Gomez et al (1995) reported no difference in prevalence of gingival banding in HIV infected and non-infected groups.[50] Pain is rarely associated with this lesion.[5] LGE has been classified by the American Academy of Periodontology as a 'gingival disease of fungal origin'.[51] Reports on the prevalence of LGE vary greatly amongst different studies. LGE is commonly associated with HIV infection in adults and seldom reported in children.[52] The prevalence of this type of gingivitis varies widely from 0 to 48 percent.[39,42,53,54] Pediatric studies reporting on this manifestation include: Flaitz et al[55] (2001)– 4 percent; Fonseca et al[34] (2000)–1.96 percent; Chan et al, 1994 [23] (0.0%); and Flanagan et al 2000[56] (32%). Ketchem et al documented gingivitis in HIV infected children as an intensely erythematous band involving the labial marginal and attached gingivae.[39] Moniaci et al reported two patients in the P2 stage with gingivitis.[42] Additionally, San Martin et al. reported a prevalence of 37 percent for gingivitis and 4.5 percent for periodontitis in a sample of 67 children infected with HIV.[47]



Figs 2.4.7A and B: Linear gingival erythema

Linear Gingival Erythema (Figs 2.4.7A and B)

Presumptive Criteria[44]

A fiery red, linear band 2-3 mm wide on the marginal gingiva accompanied by petechiae-like or diffuse red lesions on the attached gingiva and oral mucosa. The amount of erythema is disproportionately intense given the amount of plaque present. The erythema may be accompanied by bleeding during brushing and, in severe cases, by spontaneous bleeding. It is most notable on the mandibular labial gingival surfaces from cuspid to cuspid. Pain is rarely associated with linear gingival erythema.

Definitive Criteria[44]

There are currently no known criteria for obtaining a definitive diagnosis of linear gingival erythema. However, linear gingival erythema resists conventional plaque—removal therapies and oral hygiene measures. A similar clinical presentation occurs in neutropenia. Thus, clinicians should review results of a recent complete blood count and differential analysis of the white blood cells.

Salivary Gland Disease

The term 'HIV-SGD' (Salivary Gland Disease) has been used to designate diffuse enlargement of major salivary glands and/or xerostomia in HIV infected individuals.[57] Parotid enlargement has been recognized as a distinctive feature of HIV infection in children since the first descriptions of the disease (Fig 2.4.8). Parotid gland enlargement can occur in both HIV positive and HIV negative individuals. In HIV negative individuals, prevalence is low and is usually associated with conditions such as mumps in children, and anorexia nervosa in adults.



Fig. 2.4.8: Bilateral parotid gland enlargement

Parotid gland enlargement associated with HIV infection has been found both in adults and in children. In HIV infected individuals, parotid enlargement is ranked as a Group1 lesion in children (Box 2.4.1) and a Group 2 lesion in adults. This manifestation has been reported in 10-30 percent of the children with symptomatic HIV infection.[58]

Parotid gland enlargement has been recognized as a distinct feature of HIV infection in children.[38,40] It is prevalent in 0 to 58 percent of HIV infected children.[57] Katz et al (1993)[45] reported a figure of 50 percent, whilst Soberman et al (1991)[59] reported that parotid enlargement of varying degrees was seen in 10 percent of HIV children in New York. Parotid enlargement may manifest as unilateral or bilateral swellings. Typically, the enlargement is chronic and the glands are profusely swollen and firm. This manifestation is usually asymptomatic and painless. It is uncertain what the etiology of the enlargement is, but a computer tomography (CT) scan and magnetic resonance imaging (MRI) findings in HIV infected adults have described benign lymphoepithelial proliferation as the underlying cause of parotid enlargement.[60] Histologically, the enlarged parotid gland demonstrates lymphocytic infiltration, which may be caused by infection with Epstein-Barr virus (EBV) or HIV or an interaction between the two.[61]

Parotid enlargement in children is often associated with lymphoid interstitial pneumonitis (LIP) and diffuse lymphadenopathy, which probably represents a lymphoproliferative stage of HIV infection in children. It has also been associated with xerostomia. However, it is not certain whether the xerostomia is as a consequence of concurrent medication, or the parotid enlargement. Studies involving major salivary gland output in HIV infected individuals have shown a decrease in salivary output.[62,63] Some investigators have reported that as many as 13 percent of HIV positive patients complain of dry mouth.[64] The presence of parotitis is a predictor of positive prognosis and long-terms survival in HIV infected children.[65]

Parotid enlargement has been associated with a slower progression to AIDS and is hence a positive prognostic indicator.[65] The median time to death has been reported as 5.4 years among those children with parotid swelling.[32] In adults, the finding of chronic parotid enlargement is significant in that it should suggest the diagnosis of HIV infection.

Parotid gland enlargement is usually left untreated. In extreme cases however, parotid swelling may be treated with anti-inflammatory agents, analgesics, antibiotics or occasionally, steroids.[5] Parotitis resolves in many patients being treated with zidovudine; however, recurrence of the lesion may occur.[61] Occasionally, a biopsy may be necessary to rule out an infectious etiology or neoplasm in the presence of atypical findings such as unilateral involvement, acute inflammation, or a rapidly enlarging mass.

Presumptive Criteria[44]

Uni or bilateral diffuse soft tissue swelling resulting in facial disfigurement. May be accompanied by pain, and may be associated with lymphoid interstitial pneumonitis.

Oral Ulceration

Ulceration of the oral cavity may be defined as a breach in the epithelial lining of the mouth and its structures. Oral ulceration has numerous etiologies. It may manifest in both immunocompromised, and immunocompetent individuals. The occurrence of specific oral ulcerations may be a reflection of immune suppression in both HIV infected and non-infected individuals, or they may be pathognomonic of HIV disease.[66] Oral ulcers associated with HIV infection can be caused by a variety of organisms or processes.[51] Kademani et al also recommend that oral ulcers be categorized into 2 groups on the basis of diagnostic criteria and treatment protocols. The first group consists of ulcers caused by a specific organism (e.g. Herpes Simplex Virus - (HSV); Cytomegalovirus - (CMV), etc.) or associated with a neoplastic condition (e.g. lymphoma). The second group consists of ulcers which have no identifiable causative organism or process and are histologically 'nonspecific'.

Recurrent Aphthous Ulcers (Fig. 2.4.9)

Recurrent aphthous ulcers occur in approximately 2-6 percent of the adult HIV infected population and are more common among HIV infected children. Recurrent aphthous ulcers occur in several different clinical forms, usually described as minor, major and herpetiform, based on the size, number and duration of lesions present.



Fig. 2.4.9: Aphthous ulcer

Recommended therapy for isolated lesions consists of direct application of 1:1 mixture of Orabase® and topical steroids. Multiple or inaccessible lesions may be treated with dexamethasone rinses. Systemic steroid therapy may be indicated if children are resistant to topical application of medications, when they are unable to rinse or gargle medication, or when lesions are resistant to a short course of topical treatment. Because steroid therapy may exacerbate lesions of infectious etiology, correct diagnosis of aphthous ulceration is necessary before treatment.[25]

Minor Recurrent Aphthous Ulcers (Fig. 2.4.10)

Presumptive Criteria[44]

A small ulcer less than 5 mm in diameter covered with a pseudomembrane and surrounded by an erythematous halo.

Definitive Criteria[44]

A prompt response to steroid treatment confirms the diagnosis of recurrent aphthous ulcers.

Major Recurrent Apthous Ulcers (Fig. 2.4.11)

Presumptive Criteria[44]

Similar to those for minor recurrent aphthous ulceration; however, the mucosal lesions are 1 to 2 cm in diameter and may persist for many weeks. Major recurrent aphthous ulcers are painful and may interfere with mastication and swallowing. They occur on the soft palate, buccal mucosa, tonsillar area, and tongue.

Definitive Criteria[44]

Response to treatment with steroid agents.

NOTE Major recurrent aphthous ulcers have recently been associated with the use of HIV antiviral therapies such as ddC (zalcitabine).



Fig. 2.4.10: Minor aphthous ulceration



Fig. 2.4.11: Major aphthous ulceration

Herpetiform Recurrent Aphthous Ulcers

Presumptive Criteria[44]

Herpetiform lesions appear as clusters or crops of tiny recurrent aphthous ulcers 1 to 2 mm in diameter, which may coalesce. Like major recurrent aphthous ulcers, herpetiform lesions tend to occur in locations where they hinder eating and speaking, such as the soft palate, buccal mucosa, tonsillar area, and tongue.

Definitive Criteria[44]

Responds to treatment with steroid agents.

Group 2: Orofacial Lesions Less Commonly Associated With Pediatric HIV Infection

Bacterial Infections of Oral Tissues

HIV infected children are more susceptible than adults to bacterial infections, especially those involving polysaccharide- encapsulated organisms (e.g. *Streptococcus pneumoniae*). Bacterial infections in immunocompromised children are frequently severe, deep-seated and difficult to treat. Sinusitis and otitis media occur in children almost universally. Moreover, although HIV associated periodontal diseases have been thought to appear less frequently in children than in adults, recent studies indicate that this assessment may be premature.

Periodontal Diseases

Necrotizing Ulcerative Gingivitis (NUG) (Fig. 2.4.12)

Presumptive Criteria[44]

The destruction of one or more interdental papillae accompanied by necrosis, ulceration, and/or sloughing.



Fig. 2.4.12: Necrotizing ulcerative gingivitis

Destruction is limited to the marginal gingival tissues. In the acute stage (ANUG), the gingival tissues appear fiery red and swollen, and are accompanied by yellowish-grey necrotic tissue that bleeds easily. Patients experience symptoms such as bleeding while brushing, pain, and halitosis.

Definitive Criteria[44]

There are no definite criteria for either NUG or ANUG. Diagnosis must be determined clinically. Responds to systemic antibiotic treatment and local debridement.

> **NOTE** Symptoms may subside gradually over 3-4 weeks, but recurrences are common. NUG may represent an initial stage of necrotizing ulcerative periodontitis.

Necrotizing Ulcerative Periodontitis (NUP) (Fig. 2.4.13)

NUP is characterized by a localized lesion resulting in rapid loss of supporting periodontal structures and loose teeth with no pocket formation. In one patient, severe ulceration of the supporting periodontal structures and alveolar mucosa in relation to the mandibular primary central incisors was observed with Class III mobility of the two teeth. NUP is a serious oral manifestation that causes pain, spontaneous gingival bleeding, and rapid destruction of bone and soft tissue. Loss of bony support may lead to tooth mobility and even tooth loss. No unique micro-organisms have been identified. The anaerobic periodontal flora seems similar to that which causes conventional periodontitis. Although unusual in young children, severe generalized periodontal bone loss has been observed in preadolescents whose HIV infection had gone undiagnosed and untreated. Healing was successful after proper dental and medical care.



Fig. 2.4.13: Necrotizing ulcerative periodontitis

Presumptive Criteria[44]

Severe soft-tissue necrosis along with destruction of the periodontal attachment and bone over a period of time. Patients often experience spontaneous gingival bleeding or bleeding while brushing and severe, deep, aching pain in the jawbone. In most severe cases, the jaw bone may be exposed. The final stage of necrotizing ulcerative periodontitis is marked by severe gingival recession resulting from rapid bone loss and soft tissue necrosis.

Definitive Criteria[44]

There are no definite criteria for the diagnosis of NUP.

> **NOTE** Pocket formation may be minimal because of simultaneous loss of both hard and soft tissues. Tissue destruction may extend across the mucogingival junction. NUP is chronic; ulceration will be seen during active periods but may be absent during dormant periods.

Necrotizing Stomatitis (NS) (Fig. 2.4.14)

Presumptive Criteria[44]

Acute and painful ulceronecrotic lesions on the oral mucosa. Underlying bone may be exposed, or the lesion may penetrate or extend into adjoining tissues.

Definitive Criteria[44]

Histologic examination reveals nonspecific features.

> **NOTE** NUG, ANUG, NUP and NS each represent a different stage of what appears to be a single disease. Necrotising stomatitis occurs only in the most severe cases.

Seborrheic Dermatitis

Presumptive Criteria[44]

Erythema and scaling of the scalp, skin behind the ears, and nasolabial folds are particularly characteristic.



Fig. 2.4.14: Necrotizing stomatitis

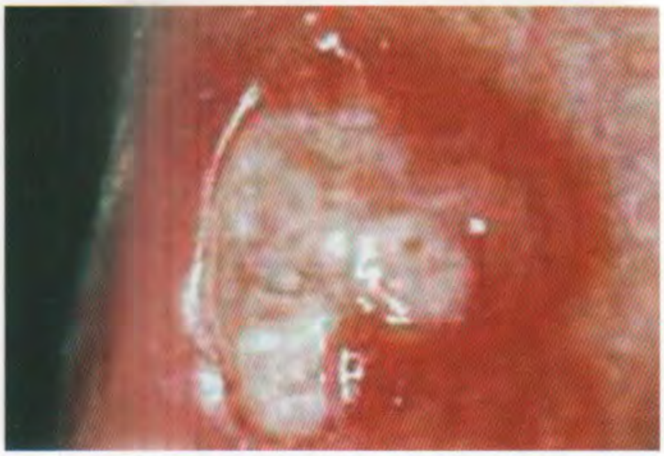


Fig. 2.4.15: Cytomegalovirus associated ulcer on the buccal mucosa

Definitive Criteria: No definitive Criteria[44]

NOTE HIV infected children experience a wide variety of mucocutaneous manifestations. Some skin diseases are due to exacerbation of childhood dermatoses (e.g. atopic or seborrheic dermatitis) or are reactions to medications. Viral, bacterial, and fungal infections are most common.

Viral Infections

Cytomegalovirus (CMV) (Fig. 2.4.15)

Presumptive Criteria[44]

Lesions associated with CMV may mimic a number of persistent oral ulcers, including aphthous ulcers, recurrent herpes simplex virus infection, necrotizing stomatitis, and ulceration. Occasionally, this infection may present as a brightly erythematous gingivitis.

Definitive Criteria[44]

A definitive diagnosis can be made through culture and biopsy.

Human Papilloma Virus (HPV) (Fig. 2.4.16)

The incidence of oral warts due to human papilloma virus (HPV) has dramatically increased in the potent antiretroviral therapy era. Studies have shown that the risk of HPV-associated oral warts is associated with a 1–log 10 or greater decrease in plasma HIV RNA level within the 6 months prior to oral HPV diagnosis, suggesting that the development of warts may be related to immune reconstitution.[67] The warts may be cauliflower-like, spiked, or raised with a flat surface. Treatment may involve surgery, laser surgery, or cryotherapy. It should be noted that HPV survives in aerosol. Topical 5-fluorouracil treatment has



Fig. 2.4.16: Human papilloma virus associated warts

been used on external lesions, but should be used with caution since it can cause hyperpigmentation. It should be noted, however, that this is a specialized treatment and should only be used by those experienced with the use of this topical medication. Lesions tend to recur after treatment.[67]

Presumptive Criteria[44]

Raised, irregular, flesh-colored lesions (warts).

Definitive Criteria[44]

Excisional biopsy. However, diagnosis is generally based on clinical appearance.

NOTE: Children with HPV infection may develop verruca vulgaris, widespread flat warts, and condylomata acuminata. The presence of condylomata in a child should alert the clinician of the possibility of sexual abuse.



Fig. 2.4.17: Molluscum contagiosum

Molluscum Contagiosum (Fig. 2.4.17)

Presumptive Criteria[44]

A virally induced lesion of the skin, mucus membranes, and rarely the oral cavity. Lesions are small, discrete and dome-shaped. Their color ranges from pearly white to skin color. In HIV infected patients, the lesions may number in hundreds.

Definitive Criteria[44]

When the core of the lesion is expressed and stained, molluscum bodies which are virally transformed epithelial cells can be seen.

Herpes Zoster (Fig. 2.4.18)

Presumptive Criteria[44]

Secondary disease or reactivation of latent varicella zoster virus. Herpes zoster is primarily a condition that affects older adults and those who are immunocompromised. Pain and paresthesia is a prodromal symptom. A well delineated unilateral maculopapular rash that becomes pustular and ulceration follows.

Definitive Criteria[44]

Cytologic examination reveals virus-infected epithelial cells. Commonly confused with recurrent herpes simplex virus infections, herpes zoster can be definitively diagnosed through virus antigen typing with laboratory immunologic tests.

Varicella

Presumptive Criteria[44]

Primary infection with the varicella zoster virus, one of the herpes viruses. A rash involving the head, neck and trunk



Fig. 2.4.18: Herpes zoster

may be accompanied by fever, chills, malaise, and headache. The rash becomes vesicular, pustular, and finally, ulcerated. With successive waves of viremia, successive crops of new lesions appear. When the oral mucus membranes are involved, evanescent vesicles precede multiple shallow ulcers.

Definitive Criteria[44]

Careful attention to history of exposure and type and distribution of lesions usually leads to a clinical diagnosis.

Xerostomia (Fig. 2.4.19)

Xerostomia is far more common in HIV infected children than HIV infected adults. It may present not only as a result of HIV infection, but also as a result of



Fig. 2.4.19: Xerostomia

medications, such as intravenous γ-globulin and antiviral drugs such as didanosine (ddI). However, no discernible difference in the average salivary flow rates has been found between HIV infected and non-infected patients. Xerostomia may appear with or without parotid swelling. Recommended therapy is generally palliative and should include more frequent oral examinations and administration of topical fluoride rinses and home rinses. Stimulation of salivary flow with the use of sugarless gum or sour candies, frequent water intake, or administration of pilocarpine may be beneficial. Use of crystal methamphetamine in xerostomic individuals is associated with rapid dental decay known as "meth mouth". The primary factor in this condition is probably xerostomia, with contributions from bruxism, poor diet, sugar cravings, and the corrosive constituents of crystal methamphetamine, i.e. lithium, muriatic and sulfuric acids, and lye.[67]

Presumptive Criteria[44]

Dry mouth and severely reduced salivary flow rates:

Definitive Criteria[44]

No definitive criteria exists for xerostomia.

GROUP 3: Orofacial Lesions Strongly Associated With HIV Infection But Rare In Children

Kaposi's Sarcoma (KS) and Non-Hodgkin's Lymphoma (Fig. 2.4.20)

HIV associated cancers such as Kaposi's sarcoma and non-Hodgkin's lymphoma are far less common in children than in adults. Kaposi's sarcoma (KS) is a spindle cell, vascular tumor that occurs in the skin, lymphoid, respiratory, and gastrointestinal tract tissue. It is a common tumor in both HIV positive and HIV negative persons living in parts of Africa.[68] The HIV sero negative form of KS is called 'endemic KS'. KS seen in HIV positive and HIV negative individuals is pathologically identical. Endemic KS is generally an indolent tumor in HIV negative adults, but it also occurs in children where it has a fulminant and often fatal course.[68] The Human Herpes Virus 8 (HHV8) has been identified in the etiology of KS.[69]



Fig. 2.4.20: Kaposi's sarcoma

Kaposi's sarcoma is the most common tumor associated with HIV/AIDS, and has been reported in 15 percent of the AIDS population. These lesions may appear anywhere in the oral cavity and range in appearance from flat to raised, and red to purple lesions.

KS as a manifestation of HIV infection in children is rare in Western countries. In Kampala, Uganda, KS is being recognized in an increasing number of children. From 1986 to 1990, 25 cases of oral lesions were documented.[38] Detection of the HHV8 genome in KS lesions in pre-pubertal Ugandan children suggests that the transmission of the virus may be non-sexual. HIV related cancers occur more commonly in adults than in children. KS is the most common HIV associated malignancy in adults and frequently presents with oral lesions. Its incidence however, has drastically decreased since the administration of HAART in HIV infection.[70] Definitive diagnosis requires biopsy. Treatment ranges from localized injections of chemotherapeutic agents, such as vinblastine sulfate, to surgical removal. Oral hygiene must be stressed. Systemic chemotherapy may be the treatment of choice for patients with extraoral and intraoral Kaposi's sarcoma.[25]

Oral Hairy Leukoplakia (Fig. 2.4.21)

Oral Hairy Leukoplakia (OHL) appears as a white, non-removable, corrugated (hairy) lesion, seen on the lateral border of the tongue and occasionally in other areas of the oral cavity. It is caused by the Epstein-Barr virus (EBV), which can be seen on electron microscopy and with in-situ hybridization. OHL is one of the most common HIV associated oral lesions in adults.[99] However, cases of OHL have been reported in patients with immune suppression other than HIV infection. Although OHL is seen in all the risk groups for HIV infection, it is not common in children.[38,40,71,72]

Hairy leukoplakia (HL) is rarely manifested in children with perinatally acquired HIV infection.[73] Studies show that this lesion is associated with intraepithelial proliferation of EBV and that multiple strains of the virus often are present in hairy leukoplakia tissues.[74] As exposure to EBV often does not occur until children are older, this lesion may not be an early manifestation in



Fig. 2.4.21: Oral hairy leukoplakia

perinatally acquired HIV infection. Among recent studies of oral lesions in HIV infected children, Katz et al have reported a 2 percent prevalence of hairy leukoplakia.[45] Hairy leukoplakia lesions must be distinguished from other white lesions as candidiasis in the oral cavity. A non invasive diagnostic method—scraping the lesion and using in situ hybridization is particularly useful in children. This lesion is used as a predictor of progression of HIV disease, and is not considered to be a premalignant lesion. OHL lesions will regress with antiretroviral therapy and concurrent improvement of cellular immunity, but recurrence is possible after discontinuing treatment.[38] Hairy leukoplakia lesions are usually asymptomatic and treatment may be elective. Some patients complain of discomfort, usually due to secondary infection. Lesions respond to treatment with acyclovir, but they tend to recur when treatment is discontinued.[5] Recommended treatment is elective since the lesion is generally asymptomatic. Diagnosis and observation, however, is important. Biopsy is unnecessary in patients known to be HIV infected and when clinical appearance is consistent with this lesion.[25]

Presumptive Criteria[44]

White, non-removable lesions with corrugated surface appearing bilaterally on the lateral border of the tongue. These lesions may appear on the ventral and dorsal surfaces of the tongue and, more rarely, on the buccal mucosa.

Definitive Criteria[44]

Presence of Epstein-Barr virus in the lesions, to be determined by laboratory histopathology and in situ DNA hybridization. If these studies cannot be performed, the lack of response to antifungal therapy may reinforce a presumptive diagnosis of hairy leukoplakia.

NOTE Because other pathologies may present histological changes similar to those seen in hairy leukoplakia, the histological analysis alone is considered insufficient to establish a definitive diagnosis. The differential diagnosis of hairy leukoplakia must include a number of other white lesions of the tongue and oral mucosa, such as idiopathic leukoplakia, hyperplastic candidiasis, white sponge nevi, geographic tongue and lesions due to biting habits or trauma.

Tuberculosis-related Ulcers

Coinfection with HIV and *Mycobacterium tuberculosis* is common in underdeveloped countries.[75] Secondary and primary TB lesions of the oral cavity are rare.

Presumptive Criteria[44]

Painless, non-healing ulceration of the buccal mucosa, hard palate, gingivae and/or tongue. Occasionally, TB may present with tongue involvement manifested as macroglossia or a mass in the cheeks. In most cases the mucosal lesions are difficult to recognize, but enlarged regional lymph nodes may call attention to the process.

Definitive Criteria[44]

A chest X-ray and a PPD test with appropriate controls should be obtained when the disease is suspected. The diagnosis is usually confirmed with acid-fast stains and cultures obtained from suspicious lesions and sputum, tracheal aspirates, bronchoalveolar lavages, gastric aspirates, lymph nodes, or tissue biopsies.

Cervical Lymphadenopathy

Enlargement of the cervical lymph nodes in children with HIV infection is usually a part of generalized lymphadenopathy. Lymphadenopathy is an early nonspecific finding in HIV infected children, and its presence alone does not meet the CDC criteria for symptomatic HIV infection.[76] Lymphadenopathy is chronic, diffused, without tenderness or signs of inflammation, and often is accompanied by hepatosplenomegaly and salivary gland enlargement. In a study reported by Chan et al, cervical lymphadenopathy was the most prevalent orofacial manifestation (54.5%) in HIV infected children in their study. This manifestation was significantly related to a decline in CD4+T cells and an increase in serum IgG.[77] A recent report from the Italian register of pediatric HIV infection, documented that lymphadenopathy was a nonspecific clinical sign in 91 percent of the long-term survivors, and 58 percent of short-term survivors, indicating that the presence of lymphadenopathy was a positive predictor of survival in HIV infected children.[61]



Fig.2.4.22: Petechiae

Petechiae (Fig. 2.4.22)

Thrombocytopenia is reported to occur in 20 to 30 percent of HIV infected patients at any age. It may appear as a result of HIV induced autoantibodies, megakaryocyte infection, aplasia, or causes unrelated to HIV.[78] Additionally, it may be related to AZT therapy, which may suppress the bone marrow including the megakaryocyte development.

Dental Caries (Fig. 2.4.23)

Children who are medically compromised and taking long-term sugar-based medications are classified as being at high risk.[79] Many children with HIV infection experience xerostomia as a side effect of antiretroviral therapy which further exacerbates their caries risk. Aside from their medical status, the absence of fluoridated water supplies or fluoride supplements, along with the presence of other factors such as the social history of the child, cariogenic diet, poor plaque control and clinical evidence of existing or past caries, add to this risk.[79] Hence, HIV infected children may be considered at high caries risk because all of the above factors are common within this medically compromised study group: Low social status, poor dietary habits, low use of fluoride, ingestion of long-term sugar-based medicines, possible xerostomia and high caries experience.



Fig.2.4.23: Dental caries

HIV infected children may be more liable to dental caries, affecting both the deciduous and the permanent dentition, than healthy subjects. However, while the frequency of caries may be higher than in healthy controls, the dmft and DMFT of HIV infected children is not always higher than that of similarly aged children in the same geographic area,[24,55,80,81] in some instances probably reflecting differences in fluoride levels in local water supplies.[55] In addition, the caries experience of HIV infected children appears to be broadly similar to that of other chronically sick children of comparable age.[80] It has been, however, speculated that HIV infected children may display a different decay pattern to that of healthy children,[82] this possibly being related to HIV associated xerostomia.[83] A greater frequency of caries in HIV infected children may be attributed to high carbohydrate and sugar intake required to provide sufficient calories in these children after failure to thrive,[81] and to the ingestion of sucrose-based medications, particularly antibiotics and antifungals[79] and also antiretrovirals, such as zidovudine.[81] Moreover, poor social status and low use of fluoride might also contribute to an increased risk of dental caries in children with HIV disease.[79] Both delayed and accelerated eruption of permanent teeth and over-retention of primary teeth (affecting 25% of patients) were observed in HIV infected children in Romania.[55] The accelerated eruption pattern may be related to concurrent or previous dental and periodontal disease.[55] The exact cause of delayed eruption of teeth is unknown, although the poor general health status of some children, particularly when there is malnutrition, may be an important cofactor.[12,55]

Treatment should include remineralization of non-cavitated, smooth-surface lesions and restorative treatment of cavitated lesions. Establishment of recall intervals should be based on caries risk status, with high-risk patients being seen more frequently. Caries risk should be reassessed at each recall visit, and future care should be planned accordingly. In addition to fluoride varnishes, therapy in adults should include pit and fissure sealants and proper use of certain sugarless chewing gums that may provide protection.[84]

The prevalence of oral lesion, which have been reported in various studies, have been summarized in Table 2.4.3.

Table 2.4.3: Comparison of studies reporting on prevalence of orofacial manifestations in children

Author	*Sample size*	*Study design*	*Prevalence OML*	*Most common lesion*	*2nd most common lesion*	*3rd most common lesion*
Barasch et al 2000	104	Longitudinal	76%	OC (28%)	LGE (22%)	x
Charloryoo et al 1998	x	x	NR	OC (59.6%)	Lymphadenopathy (41.6%)	URTI (39.5%)
Chan et al 1994	33	Longitudinal	NR	CL (54.5%)	OC (42.4%)	Ulceration, Petechiae, Delayed dental development (3.0%)
Costa et al 1998	41	Case control	NR	Cl (53.7%)	OC (29.3%)	AC (9.8%)
Del Toro et al 1996	28	Longitudinal	39.3%	PC (17.8%)	MiAU (7.1%)	Parotid swelling, Delayed dental development (3.6%)
Flaitz et al 2001	173	Longitudinal	55%	OC (29%)	Ulcers (15%)	SGD (9%)
Flangan et al 2000	38	Longitudinal	79%	CG (50%)	LGE	OC (24%)
Fonseca et al 2000	51	Longitudinal	51%	PC (21.6%)	SGD (19.6%)	EC 5.9%
Howell et al 1996	60	x	45%	OC (32%)	CG (45%)	LGE (38%)
Katz et al 1993	99	x	NR	OC (72%)	PGE (47%)	Herpes simplex (24%)
Ketchem et al 1993	47	Point prevalence	NR	OC (25.5%)	Dental anomalies (4.3%)	x
Khongkunthian et al 2001	45	Point prevalence	48.9%	EC (17.8%)	Aphthous ulcers (11.1%)	AC, OHL, Oral ulcers (6.7%)
Magalhaes et al 2001	38	x	52.6%	OC (36.8%)	AC (28.9%)	PGE (18.4%)
Moniaci et al 1993	69	Longitudinal	P	PC (26%)	EC (10%)	AC (5.8%)
Nicolatou et al 1999	15	Longitudinal	60%	OC (60%)	EC (10%)	AC (5.8%)

NR = Not reported in study, p = Present for column, x = Absent for column;
PC = Pseudomembranous candidiasis; EC = Erythematous candidiasis; OC = Oral candidiasis; AC = Angular cheilitis;
PGE = Parotid gland enlargement; OHL = Oral hairy leukoplakia; OU = Oral ulceration; CL = Cervical lymphadenopathy;
MiAU = Minor aphthous ulceration; CG = Conventional gingivitis; MTCT= Mother to child transmission; ART= Anti-retroviral therapy;
OML = Oral mucosal lesions

Importance of Orofacial Lesions in HIV Infection

Oral lesions can not only indicate infection with human immunodeficiency virus (HIV), they are also among the early clinical features of the infection and can predict progression of HIV disease to acquired immunodeficiency syndrome (AIDS).[85-87] They can be, therefore, used as entry or end-points in therapy and vaccine trials and can be determinants of opportunistic infection and anti-HIV therapy. They can also be used in staging and classification systems.

Oral manifestations are the earliest and most important indicators of HIV infection. Seven cardinal lesions: Oral candidiasis, hairy leukoplakia, Kaposi's sarcoma, linear gingival erythema, necrotizing ulcerative gingivitis, necrotizing ulcerative periodontitis and non-Hodgkin's lymphoma are strongly associated with HIV infection and have been identified universally. These lesions may be present in up to 50 percent of people with HIV infection and in up to 80 percent of those with a diagnosis of AIDS.[7] These oral lesions are usually clearly visible and can be diagnosed reliably from the clinical features alone.[88] The lesions parallel the decline in numbers of CD4+ cells and an increase in viral load, and are independent indicators of disease progression. In cases where a person's HIV status is unknown, the lesions provide a strong indication of the presence of HIV infection. For this reason, the presence and development of oral lesions are used as entry criteria and end points for prophylaxis and therapy, which explains the weight given to these lesions in HIV prevention and intervention programes.

Oral Lesions as An Early Sign of HIV Infection

The main factors associated with the development of oral lesions, and especially oral candidiasis, is the CD4+ count.[10] Various studies have demonstrated that oral

lesions are more common in persons with HIV infection than in those who are HIV negative.[32] In a Tanzanian study Schiødt et al (1990) showed that 85 percent of the sample who were diagnosed with oral lesions were later confirmed as HIV infected.[89] Similar studies conducted in Belgium, Greece and Zaire report similar findings.[90] Studies regarding oral HIV infection as an AIDS-defining condition have been reported.[91] There seems to be a growing consensus that oral hairy leukoplakia (OHL) and Kaposi sarcoma (KS) in particular, are highly suggestive of HIV infection. These lesions are found in adult HIV infection. However, prevalence studies on oral lesions associated with HIV infection in children do not demonstrate the same lesions which are ranked 'Group 3' (lesions strongly associated with HIV infection but rare in children) of the Consensus Classification of orofacial lesions associated with pediatric HIV infection.

Oral Lesions as a Predictor of Disease Progression

Orofacial manifestations are used as predictors of progression of HIV disease to AIDS.[45,65,91,92] These manifestations may indicate the degree of immunosuppression while some lesions are AIDS-defining conditions.[91] Table 2.4.4 presents the prognostic significance of oro-facial manifestations in pediatric HIV infections.

A study by Barasch et al (2000), however, indicated that oral lesions were not necessarily good indicators of immune suppression.[93] Several other studies have emphasized the prognostic significance of oral candidiasis[91] and hairy leukoplakia[94] as predictors of immuno supression and AIDS-defining conditions in adults. Similar studies documenting the prognostic implications of oral lesions in HIV seropositive children have emerged recently.[45,65,92] Oral candidiasis has been associated with immune suppression, a more rapid progression of HIV infection to AIDS, a more advanced stage of AIDS, and decreased survival.[55] Low CD4 counts for age are valuable markers of immunodeficiency and are useful indicators of risk for developing opportunistic infections in HIV infected children.[92] The onset of oral candidiasis and oral hairy leukoplakia is heralded by a sustained reduction in the CD4+ blood cell count associated with a sharp increase in viral load.[10]

A study by Chan et al[23] investigated the relationship of oral manifestations to parameters of immune function and the CDC stage in children born to HIV positive women. A review of 33 charts of these women revealed that cervical lymphadenopathy and oral candidiasis were the most prevalent oral manifestations. Both of these lesions were associated with a decline in the number of CD4+ T cells and an increase in serum IgG. Only oral candidiasis was related significantly to the CDC staging of HIV disease, with the lesion being more prevalent in children with symptomatic HIV infection. In another study by Moniaci et al,[95] the relationship of oral mycotic infections to CDC stage and level of CD4+ T cells in children with perinatally acquired HIV infection was investigated. The authors showed that a significant relationship exists between oral candidiasis and declining CD4+ T cell and neutrophil (PMN) count in HIV infected children. Also, they observed that mycotic lesions and other oral lesions are more frequent in P2 CDC-stage patients.[95]

De Martino,[65] Tovo et al[92] in 1991 showed that in infants with perinatal HIV infection, immunologic abnormalities correlate with the clinical condition and are predictive of clinical outcomes rather than infection status. In this study, all children who had clinical symptoms had earlier and more profound immunological modifications than children who remained symptom-free.[65,92] De Martino stated that children infected with HIV do not necessarily develop AIDS by a set pattern, but can be

Table 2.4.4: Prognostic value of orofacial manifestations in pediatric HIV infection

Lesion	*Comment*	*Reference*
Orofacial Manifestation	Correlation of orofacial lesions with CD4+ cell counts and clinical staging	Chan et al (1994)
	P-2 patients had displayed a higher prevalence of oral lesions than P-1 patients ($p = 0.04$)	Del Toro et al (1996)
Oral candidiasis	Presence and period of infection may be diagnostic of HIV infection	De Martino (1994)
	Pseudomembranous candidiasis is significantly related to severe immunologic impairment	Moniaci et al (1993)
	Oral candidiasis was associated with the most rapid rate of progression to death. Median time from presentation of lesion to time of death was 3.4 years	Katz et al (1993)
Oropharyngeal candidiasis	Progression of HIV disease to AIDS	Ramos Gomez et al (1996), Scarlatti (1996), Flaitz et al (1999)
Parotid gland enlargement	Associated with long-term survival in HIV positive children	Ramos-Gomez et al (1996)
	Associated with a less rapid rate of progression to death. Median time from first presentation of enlargement to death is 5.4 years	Katz et al (1993)

divided into long and short-term survivors. A study reported by De Martino from the Italian register for HIV infection in children showed that a CD4 cell decrease early in life can be predictive of survival outcome. Additionally, it was observed in the study that lymphadenopathy and parotitis were more frequent clinical findings in long-term survivors (LTS) than short-term survivors (STS) and that these signs were positive predictors of survival in children.[65]

Rubenstein and Calvelli agreed with de Martino that many children with early lymphadenopathy and parotitis continued to display only minor clinical symptomatology and had the most favorable prognosis.[96] On the other hand, children having onset of opportunistic infections early in their disease course had poor prognosis. Katz et al. in a longitudinal study determined that the median time from the development of lesion to death was shorter for oral candidiasis than for parotid enlargement. They were of the opinion that, because of the strong association between oral lesions and survival outcomes, candidiasis and parotid enlargement should be incorporated into prognostic indices and decisions regarding therapy for HIV infected children.[45] Scott et al. reported that age at diagnosis and patterns of disease (sequence of appearance of clinical manifestations such as Lymphoid Interstitial Pneumonitis, encephalopathy and, recurrent candida esophagitis) are important prognostic factors for survival.[97]

Ketchem et al., in a survey of oral findings in 47 HIV seropositive children, found that oral candidiasis was present in 60 percent of the children in P-2 stages and 23 percent of the children in P-0 stages. Most candidial lesions were creamy white or yellowish pseudomembranous plaques and usually affected large areas of the oral mucosa in P-2 children, whereas lesions in P-0 children were generally small and localized. When correlating severity and frequency of candidiasis to immunological parameters, their data indicated that as CD4 lymphocyte cell depletion progressed, the frequency and severity of candidiasis increased.[39]

Non-Hodgkin's lymphoma, the most common lymphoma of the oral cavity, is suggestive of a declining immune system and has a poor prognosis. The mean CD4+ cell count of patients diagnosed with non-Hodgkin's lymphoma is less than 100 cells/mm^2, and the mean survival time is between 6 and 9 months.[98]

There is a correlation between delayed tooth eruption and the progression of pediatric HIV to AIDS.[99] Caries experience in HIV infected children is reported to be considered greater than that in the general pediatric population. Caries experience increases with a decreasing CD4+ count and moderate-to-severe immune suppression.[100]

Oral Lesions as Markers for Clinical Drug Trials

Oral lesions may be useful during clinical drug trials. They may be used as markers for entry into-or end points, of clinical drug trials (UCSF AIDS Research Institute, 2000).

Oral Lesions for Disease Classification

Oral lesions form part of the criteria for clinical staging of HIV disease (CDC, 1994). The presence and development of oral lesions in HIV infection emphasizes the importance of a thorough oral examination at every stage in the diagnosis and management of all HIV positive patients, as well as those thought to be infected or at risk.

Role of Dental Professionals

Dental Management of HIV Infected Children[101]

Providing proper preventive oral health care and treatment of oral disease as part of good primary medical care decreases the risk of oral infection, eliminates pain and suffering, and promotes good oral and general health in all HIV patients. Another role of treatment of oral disease is primary detection of HIV infection. For example, candidiasis which persists after early infancy may indicate undetected HIV infection.

Normal oral/dental problems of infancy, childhood and adolescence are often exacerbated in the case of patients with HIV infection, resulting in serious and debilitating oral health problems. Medications used to combat HIV or opportunistic infections can similarly cause painful and debilitating oral problems such as ulcers and dental caries that can result in dental abscess. The resulting inability to attain adequate nutrition raises the potential for dehydration and weight loss. Low socioeconomic level, dysfunctional families, and neglect are considered high-risk factors for oral disease, as is the poor oral health of the parent/caregiver.

Given the circumstance of most children and adolescents with HIV, many risk factors for dental and oral disease are prevalent. Therefore, oral/dental preventive education is recommended to begin during the prenatal period. Preventive care should start with the infant and include the caretaker. Preventive measures provided by the child's caregiver and the medical-dental team are especially critical for the child with HIV infection. Dental sealants, optimal systemic and topical fluoride, and fluoride varnish supplementation are keys to preventive strategy.

Dental therapy based on effective home care and management of nutrition and medication can give a sense

of accomplishment to caregivers who may feel ineffective in combating the child's illness. The patient's oral hygiene and the condition of the soft tissues usually reflect the degree of the caregiver's and the patient's ability to adhere to the specified home care regimen. The age appropriate dental intervention is given in Table 2.4.5.

HIV infection does not necessitate changes in the treatment plan for a child or adolescent. However, effects of HIV infection on the pediatric patient and the patient's family may alter the oral health care provider's approach to treatment. Updating of medical and psychosocial summaries is an important part of treatment of chronically ill patients and should be performed at recall visits. In the overall healthcare management of the patient, the oral health care provider should give restorative care and develop a suitable prevention program tailored to the profile of the individual child. HIV status in itself is not a reason to alter a treatment plan.

Table 2.4.5: Oral health preventive strategies by Age[101]

Age group	*Preventive strategies*
Infants	Supervised use of bottles for feeding or pacification, management of cariogenic medication
Children	Dental sealants, optimal systemic and topical fluoride, fluoride varnish supplementation, *management* of nutrition and medication, low frequency and chronicity of fermentable carbohydrate intake (e.g. juices, milk, dietary supplements)
Adolescents	Removing residue of food and medicine through rinsing with water or mechanical cleansing, management of nutrition and medication, addressing barriers that prevent adolescents from accessing care.

Control of Cross Infection

A major concern for any clinician treating HIV infected patients is to minimize the risk of exposure for themselves, their staff, and other patients. Dental procedures frequently cause bleeding and exposure to infected blood is a known means of HIV transmission. Saliva has not been shown to transmit HIV in a dental setting, but the potential for exposure to bloody saliva does exist. To reduce the risk of disease transmission, the American Dental Association (ADA), the Occupational Safety and Health Association (OSHA), and the CDC have set standards of infection control for dental health care personnel (DHCP). The following summary highlights regulations based on CDC recommendations.[102]

Infectious organisms can be spread through several routes in the dental office: direct skin or percutaneous exposure to blood, oral fluids, or other secretions; indirect contact with contaminated instruments, operatory equipment or environmental surfaces; and/or contact with airborne contaminants present in either droplet spatter or aerosols of oral and respiratory fluids. Infection via any of these routes requires that all of the following conditions be present (commonly referred to as "the chain of infection"): a susceptible host; a pathogen with sufficient infectivity and numbers to cause infection; and, a portal through which the pathogen may enter the host. Effective infection control strategies are intended to break one or more of these "links" in the chain, thereby preventing infection. HIV can be transmitted through sharps injuries or direct contact with open wounds on the skin or mucous membranes. There is no evidence that HIV is transmitted via the airborne route or insect vectors. Because individuals with an infectious disease cannot always be identified through history review or physical examination, the CDC recommends that DHCP follow a standard set of precautions for all patients at all times. The use of these precautions has reduced the chance that an infection can be transmitted in the dental operatory. Standard precaution procedures are widely publicized and describe techniques used to reduce contact with organisms (breaking the chain at the portal of entry) and the potential transmission of infectious agents. These precautions protect DHCP from all blood borne organisms, including HIV.

DHCP must wear protective devices designed to protect personnel and patients in dental care settings. Medical gloves (latex or vinyl) must be worn when there is any potential for coming into contact with blood, blood contaminated saliva, or mucous membranes. Nonsterile gloves are appropriate for examinations and other non-surgical procedures; sterile gloves should be used for surgical procedures. Before treatment of each patient, DHCP should wash their hands and put on new gloves; after treatment or before leaving the dental operatory, DHCP should remove and discard gloves, then wash their hands. DHCP always should wash their hands and re-glove between patients. Chin length plastic face shields or surgical masks and protective eyewear should be worn when splashing or spattering of blood or other body fluids is likely, as is common in dentistry. Masks should be changed between patients or when wet or soiled. Eyewear should be washed with an appropriate cleaning agent and, when visibly soiled, disinfected between patients. Protective clothing (reusable or disposable gowns, laboratory coats, or uniforms) should be worn when clothing is likely to be soiled with blood or other body fluids. Reusable protective clothing should be washed, using a normal laundry cycle, according to the instructions of detergent and machine manufacturers. Protective clothing should be changed at least daily or as soon as it becomes visibly soiled.

Impervious-backed paper, aluminum foil, or plastic covers should be used to protect items and surfaces (e.g. light handles or X-ray unit heads) that may become

contaminated by blood or saliva during use and that are difficult or impossible to clean and disinfect. These coverings should be discarded and replaced between patients. These precautions significantly reduce the risk of exposure to HIV when used consistently and correctly. Unfortunately, accidents can happen, should a blood exposure occur, the CDC has developed guidelines for postexposure prophylaxis (PEP) in case of such an eventuality.

Conclusion

HIV disease and its treatment is an ever-evolving discipline within medicine. It requires that the dental practitioner to be familiar with the current treatment methods for this expanding subset of patients and the challenges that they bring. Regular oral examination may alert the clinician to a change in the status of HIV infection and therefore prompt appropriate care, whether it is the curative treatment of opportunistic infections or palliative care in the later stages of the disease.

Pediatric dentists can play a role both in the early detection of HIV related oral lesions and in training pediatricians to recognize these oral lesions. The pediatric dentist should collaborate with other health professionals to correlate oral lesions, immunological parameters, and other clinical findings to provide proper prophylactic therapy and to improve the survival of HIV infected children. The pediatric dentist should be aware about the fact there is no cure for HIV disease and the serious nature of the infection can nevertheless be forgotten, even if it is well masked by successful antiretroviral therapies. Abolishing the stigma and taboo associated with the disease and increasing AIDS awareness is the need of the hour.

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2.5

Neurological Manifestations of HIV in Children

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Introduction

The nervous system is a frequent target of HIV infection, and the consequences of nervous system involvement in HIV infection are serious. Nervous system involve ment typically occurs in conjunction with profound immunosuppression and in the presence of other AIDS-defining illnesses. HIV associated neurological disorders can however be the first problems with which children and adults with AIDS appear for treatment. Various abnormalities of the central nervous system (CNS) and peripheral nervous system (PNS) are associated with HIV and AIDS. These abnormalities may be attributable to the following causes: HIV infection, complications related to immunosuppression, neurotoxic effects of antiretroviral treatments, and other systemic complications of HIV that affect brain function. Neurologic disorders in people with HIV infection include peripheral neuropathies (nerve disorders that affect the limbs or feet and hands), Myelopathy (disorders of the spinal cord), focal cerebral mass lesions (brain tumors such as CNS lymphoma), CNS complications of opportunistic infections, vascular (blood vessel) abnormalities, seizures, and encephalopathies. Developmental delays and regressions are also important CNS-related problems in HIV infected children.

Neurological dysfunction in the setting of pediatric HIV infection is believed to be caused by an active and primary infection of the brain by HIV. Infection is persistent and probably occurs shortly after birth. In children with perinatal infection, clinical signs of neurological dysfunction may appear as early as 2 months of age and as late as 5 years of age or older.

The natural history of HIV encephalopathy in the era of HAART is not known. Previous longitudinal studies suggest three distinct neurologic and developmental courses:[1]

1. Rapid progression.
2. Steady, subacute progression.
3. Static neurologic deficits.

Other factors, such as *in utero* exposure to drugs, also may have an effect on neurological function. As children with HIV infection reach adolescence, they may retain sequelae of early neurologic insults. In addition, HIV infected adolescents, whether perinatally or behaviorally infected, are at risk for the same neurologic complications seen in adults with HIV. As some children and adolescents who have not responded to HAART become older and more severely immune compromised, complications, such as opportunistic infections and intracranial tumors, may become more prevalent. Children with HIV infection can develop neurological illness in the same manner as noninfected children. Many children at risk for HIV infection are also at risk for developmental delays and neurological deficits. In some cases, children and adults with HIV suffer similar neurologic and psychiatric manifestations. The ongoing growth and development of children, however, sometimes leads to unique nervous system presentations of HIV disease in these patients. In this chapter, we focus on neurological and psychiatric manifestations of HIV as they relate to pediatric patients.

Epidemiology

The world health organization (WHO) estimated that >39 million persons worldwide were living with HIV infection at the end of 2004, including 2.2 million children <15 years old. More than 90 percent of HIV infected individuals live in developing nations. Sub-Saharan Africa accounts for the fastest growing epidemic, with almost 90 percent of the world's total population of HIV infected children. India and Thailand dominate the epidemic in Southeast Asia, with more recent expansion into Vietnam, China and Cambodia.[2]

The true incidence of central nervous system involvement is not known, although it is thought to occur in most HIV infected children and its incidence in children is at least three times more than that in adults.[3] HIV encephalopathy is especially common in HIV

infected children who present in early infancy and have rapid downhill course. The risk of HIV encephalopathy is also correlated directly with the severity of HIV related symptoms, depression of CD4+ counts and p24 antigen levels in the mother. The cumulative incidence of HIV-1 related encephalopathy at 7 years postinfection was noted to be 16 percent in children and the incidence of encephalopathy was 9.9 percent in the first year of life, 4.2 percent in the second year and less than 1 percent per year thereafter.[4] This underscores the fact that HIV encephalopathy can occur very early in the course of HIV infection and that 88.1 percent of children who develop encephalopathy do so within first two years of life. The incidence of CNS involvement in perinatally infected children is 50 to 90 percent in developing countries but lower in developed countries, with a median onset at 19 months of age. This may range from subtle developmental delay to progressive encephalopathy with loss or plateau of developmental milestones, cognitive deterioration, impaired brain growth resulting in acquired microcephaly and symmetric motor dysfunction. HIV encephalopathy develops in 30 to 60 percent of HIV symptomatic children and it may be the first symptom in 12 percent of HIV positive children.[5] Prior to the introduction of highly active antiretroviral therapy (HAART) in 1996, the rates of neurological dysfunction in children with symptomatic HIV infection were estimated to range from 30 to 50 percent for progressive encephalopathy and close to 90 percent for static encephalopathy. Since the advent of HAART, the rates of progressive encephalopathy found in clinical practice are much lower (approximately 5 to 10%). Because of early treatment and ongoing clinical monitoring, neurological symptoms are identified early and therefore tend to be less severe.

Pathophysiology

HIV has been found in the brain and spinal fluid of children infected by HIV. Microglia, astrocytes, oligodendroglia, and cells of the monocyte-macrophage lineages are known to have CD4+ receptors, allowing for direct infection by the virus.

A selective barrier (the blood-brain barrier or BBB) between circulating blood and brain tissues prevents many damaging substances from reaching the brain. Certain compounds readily cross the BBB; others are completely blocked. HIV has the ability to cause changes in the BBB and to enter the CNS. The neurons themselves are not infected by HIV, but neuronal function is indirectly impaired via complex mechanisms. Monocytes and microglial cells serve as the main CNS reservoirs for HIV. Once infected, these cells secrete a number of substances (such as TNF-alpha and nitric oxide) that are toxic to the brain.

HIV infected microglial cells secrete chemokines (mainly MCP-1) that amplify recruitment of HIV infected monocyte, leading to a self-perpetuating feedback loop.[6] Some of HIV's effects on the brain occur without the virus itself having to cross the BBB. The viral coat protein gp120 can enter the CNS independent of the rest of the virus and is directly neurotoxic. Brain endothelial cells react to substances associated with HIV infection, such as Tat and cytokines, by releasing neurotoxic substances at the surface abutting the brain.[7] Since HIV does not directly infect neurons, its effects on the peripheral nervous system (PNS) are also related to indirect effects of infection. Neurotoxic side effects of antiretroviral medications also have a major effect on the PNS.

The neurological manifestations may be effected directly by the virus or through cells of macrophage lineage and toxic cytokines (Fig. 2.5.1). Developmental delay (motor as well as cognitive) is a common feature. The encephalopathy may manifest suddenly as a loss of attained milestones or failure to attain new milestones. This may be interspersed with periods of relative stability or rapid deterioration. Other neurological manifestations include pyramidal tract involvement (spastic paraparesis, hypertonicity, hyperreflexia), static encephalopathy with developmental delay without loss of previously attained milestones, progressive encephalopathy with progressive deterioration of milestones and skills, acquired microcephaly, seizures, behavioral decline and cerebral arteriopathy with intracerebral aneurysm.[8,9]

Although most affected children do not have an identifiable pathogen other than HIV, other CNS processes like opportunistic infections, inflammatory disease, vascular disease or neoplastic process can cause encephalopathy.[10] Diffuse cortical atrophy, attenuation of white matter, ventricular dilatation, intracerebral calcification (especially in the basal ganglia), etc. CSF

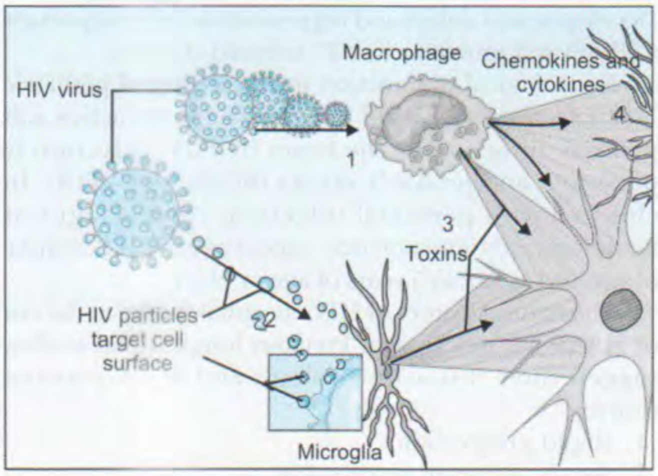


Fig. 2.5.1: Showing mechanism of encephalopathy

studies are required for diagnosing opportunistic infections and neoplasm. Abnormalities in neurophysiologic tests like the EEG and BAEP have been shown to be reliable tools for the diagnosis of HIV encephalopathy.[11] In a study, the severity of cortical atrophy appeared to reflect the level of viral load in the CSF while such an association was not observed with intracerebral calcifications, suggesting a different neuropathologic process.[12]

The presence of hepatomegaly, splenomegaly, or lymphadenopathy in the first 3 months of life and increased viral load increase the likelihood of development of HIV encephalopathy. In the early postnatal period, high viral load and lower CD8+ T-lymphocyte percentage (<20% CD8+ T-lymphocytes) have a higher risk of developing neurological impairment.[13] Being a manifestation of advanced disease, encephalopathy increases the risk of death 28-fold. Over half of the patients succumb to the illness within 3 years of diagnosis and the median survival rate in patients with HIV encephalopathy is about 11 months from the diagnosis.

Neurological Complications and Management

HIV can affect both central as well as peripheral nervous system. Clinical manifestations vary according to the age and the site of affection. There is wide range of spectrum ranging from impaired brain growth in children less than 2 years to progressive motor dysfunction, neurodevelopmental decline, seizures, static or progressive encephalopathy, myelopathy, opportunistic infections, stroke, different mass lesions including tumors and many others. CNS manifestations can be a presenting feature of HIV infection in children. One should suspect HIV infection in children presenting with neurological manifestations and growth failure. The involvement of other organ systems is variable and CNS involvement may be the solitary manifestation of HIV infection. Absence of other systemic features of HIV infection does not eliminate the possibility of HIV encephalopathy. Hence, one should undertake diagnostic study for HIV infection in a child with unexplained neurological abnormality. Pediatricians will have to be alert to the possibility of HIV as an etiological agent in infants and children presenting with mental subnormality and unexplained neurological deficits.

Baseline Neurological Evaluation

Recommendations: At routine visits, the primary care physician should be particularly vigilant for the appearance of the following conditions

- Developmental delay or loss of previously acquired milestones
- Microcephaly/deceleration in head growth
- Abnormal tone and reflexes (especially clonus and cross adductor reflex)
- Focal findings
- Speech and language delay.

A baseline neurological consultation should be obtained for all children with developmental delay or neurological signs and symptoms (e.g. focal weakness, seizures, altered mental status or microcephaly) and for any HIV infected child with a high viral load (>100,000 copies/ml) at baseline.

The neurological specialist should discuss correlation and interpretation of neurologic examination and diagnostic studies with the primary care physician.

A routine ophthalmologic evaluation, including a yearly retinal examination, should be performed in all HIV infected children. Clinicians should be aware that HIV infected children with significant immune suppression are at risk for ocular infections, including CMV retinitis, toxoplasmosis, and herpes infections.

The necessity and timing of further evaluations should be determined by the following:

- Severity of neurological involvement at the time of initial assessment
- Value of repeated neurological examinations in terms of available therapeutic intervention and prognostic measures
- Appearance of new neurological symptoms.

Children with well-controlled HIV disease and isolated developmental delays without other neurological findings should be reassessed 3 months after detection of the delay. If there is no change in neurological examination and development is proceeding, follow-up should occur according to routine neurological care practice.

The purposes of a neurological evaluation are as follows:

- Identification and documentation of abnormal neurological findings
- Identification of non HIV related neurological illness
- Categorization, when possible, of the neurological course the patient seems to be following (Rapidly progressive, subacute, or static).

The frequency of neurological reassessments for patients with developmental delays will vary according to status of HIV disease and neurodevelopemental status.

Specific Complications and their Management

HIV Encephalopathy

Recommendation: HIV should be considered in any child with progressive neurological deterioration who

has not been previously tested for HIV or who might have it despite a previous negative test. In the era of neonatal HIV screening programs, HIV encephalopathy is rarely the initial mode of HIV presentation in infected children in the United States.

Presentation

Progressive encephalopathy usually occurs in children with documented HIV infection and symptomatic disease. Progressive neurological dysfunction associated with HIV resembles a white matter neurodegenerative disorder. Most commonly, evidence of underlying HIV progression, such as immunologic compromise, coincides with onset of symptoms of encephalopathy, but because of possible compartmentalization of HIV in the central nervous system (CNS) (i.e. a sequestered reservoir of actively replicating HIV in the CNS), HIV encephalopathy may occasionally occur in well-controlled, otherwise asymptomatic HIV infected individuals. Regardless of mode of presentation, HIV encephalopathy rarely, if ever, exhibits focal neurological signs.

Diagnosis

a. **Clinical Signs Associated with Progressive HIV Encephalopathy**

- **Impaired brain growth.** In children <2 years of age, impaired brain growth manifests as deceleration of head growth or acquired microcephaly. In older children, it manifests as cerebral atrophy on neuroimaging (see *Radiological Findings Associated With Progressive HIV Encephalopathy* described below).
- **Progressive bilateral pyramidal tract signs.** These include bilateral tone abnormalities and onset of pathologic reflexes (hyper-reflexia and clonus), chiefly affecting the legs. Progressive motor dysfunction may result in a spastic diparesis, which, if severe, may interfere with ambulation. If left untreated, motor deficits may progress to a spastic quadriparesis with pseudobulbar palsy. However, with effective ARV therapy, this outcome is seldom encountered. Hypotonia with pyramidal tract involvement is described early in the course of encephalopathy in young children. Ataxia and Parkinsonian rigidity are uncommon signs and are seen only in very advanced CNS disease.
- **Developmental delay, loss of motor milestones, or cognitive impairments.** In young children, HIV encephalopathy may manifest as stagnation in development or loss of developmental milestones. Elder children and adolescents may develop HIV dementia indistinguishable from that described in adults.[14] Cognitive impairments are almost always detected but may be subtle. It is therefore useful to have baseline psychometric data obtained when the child's HIV disease is well controlled to enable detection of a decline in mental or motor performance. HIV dementia may occur with or without motor signs or psychiatric manifestations, such as psychosis.

b. **Laboratory Evaluations**

- **Cerebrospinal fluid.** Cerebrospinal fluid (CSF) parameters in children with HIV-1 infection are usually normal and, thus, are usually not assessed unless an opportunistic infection is suspected. In the absence of opportunistic infections, CSF abnormalities are nonspecific and reveal a predominantly lymphocytic pleocytosis and elevated protein levels that are rarely >100 mg/dL. CSF viral load is not routinely obtained for diagnostic purposes. Its utility is limited because of a significant overlap in CSF viral load among children with and without encephalopathy; however, levels above 10^6 copies/mm^3 have been more strongly associated with HIV dementia.[15]
- **Radiological Findings Associated with Progressive HIV Encephalopathy (Fig. 2.5.2).** Diffuse cerebral atrophy manifested as enlargement of subarachnoid space and ventricles is the most common neuroimaging finding. Foci of demyelination also may be seen, usually in the centrum semiovale or parieto-occipital white matter. Frontal lobe or basal ganglia enhancement and calcifications are late manifestations and occur primarily in symptomatic infants. Because of its greater sensitivity in detecting demyelination, MRI is the preferred brain imaging modality. However, because radiographic findings may lag behind the clinical symptoms, MRI can be normal early in the course of HIV encephalopathy. CT

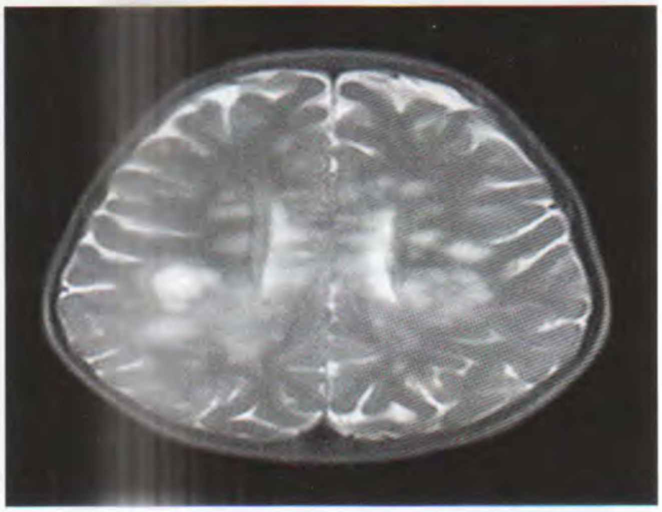


Fig. 2.5.2: Demyelinating disease

scan, in addition to MRI, may be of use in settings of advanced disease to detect calcification.

Treatment

Recommendations: HIV encephalopathy should be treated with the same ARV agents used to treat symptomatic HIV disease, with the goal of achieving low to undetectable viral load and reversal of immune suppression.

HIV infected children with neurologic impairments and developmental delays should be referred to early intervention programs.

With effective response to HAART (decreased viral load and restoration of immune function), arrest of HIV encephalopathy and gradual resolution of the neurological signs and symptoms usually follow. Clinical trials are assessing the efficacy of combination therapy comprised of reverse transcriptase and protease inhibitors. The use of HAART has resulted in decreased morbidity and mortality and diminished progression to AIDS.

Infections of the Central Nervous System

Recommendations: A pediatric HIV Specialist should be consulted whenever a central nervous system infection is suspected. Various etiologic agents should be excluded via lumbar puncture and CSF testing, unless contraindicated (Table 2.5.1). The true prevalence of CNS infections (HIV related and opportunistic) in HIV infected children is not known, but it is thought that such infections are much less frequent in children than in adults. The neurological impairment most frequently observed in children is due to HIV infection of the CNS rather than to opportunistic infection or CNS tumors. However, several distinct infections in immunosuppressed children with neurological dysfunction should be considered (Table 2.5.1).

Table 2.5.1: Laboratory evaluations for children with acute CNS manifestations

Blood	Lumbar puncture (unless contraindicated)
1. Complete blood count (CBC) 2. Blood culture 3. Electrolytes 4. Toxicology screen 5. Toxoplasmosis serum antibody 6. Cryptococcal antigen and culture	1. Opening pressure 2. Gram stain 3. Glucose 4. Protein 5. Cell count 6. Bacterial culture 7. Cryptococcal antigen and culture 8. PCR for EBV, VZV, CMV, HSV 9. viral, fungal and mycobacterial culture 10. VDRL

Cryptococcus Neoformans

In the pre-HAART era, cryptococcosis was relatively common in adults with AIDS but uncommon in children with AIDS (7 vs. 1%, respectively).[16]

Presentation

Symptoms of intracranial Cryptococcosis may include headache, fever, meningismus, focal findings, or subtle neurological dysfunction. Localized extra neural lesions may also occur in the liver, lungs, lymph nodes, and elsewhere.

Diagnosis

Recommendations: Isolation of Cryptococcus neoformans by culture, serum, and CSF Cryptococcal antigen test, or histological examination of tissue specimens should be performed to obtain a definitive diagnosis. Cryptococcal meningitis should be considered in any HIV infected patient who has new neurological findings and should be excluded by lumbar puncture. CSF antigen testing is a useful test for diagnosis and for following response to therapy. Detection of Cryptococcal capsular polysaccharide (Cryptococcal antigen) correlates well with culture results, although several cultures may be needed to confirm the diagnosis. Serum antigen may be tested if CSF is not available.

Treatment

Recommendations: Treatment for Cryptococcosis should be initiated if the organism is identified by stain or by increased levels of Cryptococcal antigen (Table 2.5.2). Waiting for culture results is not advisable before initiating therapy because it may take days or weeks to grow. Cryptococcal meningitis should be treated with Amphotericin B (with or without Flucytosine) or

Table 2.5.2: Standard and alternative drug regimens for treatment of Cryptococcosis

Standard regimen
Amphotericin B intravenously (0.7-1.0 mg/kg per day) of the standard preparation or
Liposomal Amphotericin (3-5 mg/kg per day) in once daily dose for 2 weeks or until clinically stable
with or without
5-fluorocytosine (100-150 mg/kg per day po), divided into four daily doses for 2 weeks or until clinically stable, then
Fluconazole (10-20 mg/kg IV or PO for 1 day up to 800 mg, then 5-10 mg/kg per day up to 400 mg indefinitely)
Alternative regimens
For very mild disease:
Fluconazole alone for 6-10 weeks
For very severe disease or in severely immune deficient children: Amphotericin B+5-fluorocytosine for 6 weeks prior to beginning Fluconazole suppression

Fluconazole depending on severity of disease and immune suppression (Table 2.5.2 for dosing).

Therapeutic lumbar punctures should be used to control symptoms of increased intracranial pressure secondary to communicating hydrocephalus caused by Cryptococcal meningitis.

Because HIV infected patients cannot be cured of Cryptococcosis, most patients should be maintained on lifelong chronic therapy.

Clinical and Laboratory Monitoring

Recommendations: The neurological status of patients with Cryptococcosis should be monitored daily. Lumbar puncture should be repeated within 1 week (sooner if clinically indicated), and Cryptococcal antigen level should be monitored. Antigen level should decrease with successful therapy. Opening pressure should be measured at each lumbar puncture. For patients receiving Amphotericin B, complete blood count and tests for electrolytes, BUN, Creatinine, and liver function should be performed at least once weekly to monitor for toxicities and more frequently at the beginning of therapy.

For patients receiving 5-fluorocytosine, complete blood count, platelet count, Creatinine, and serum liver enzyme levels should be obtained. Serum drug levels should be monitored, if available. A patient with Cryptococcosis may be discharged from the hospital when neurological status, especially intracranial pressure, is stable and adequate arrangements have been made for therapy at home.

After successful therapy for Cryptococcal meningitis, the patient should be maintained on lifelong suppressive therapy. Suppressive therapy regimens include daily oral Fluconazole or weekly intravenous Amphotericin.

Toxoplasma Gondii

CNS toxoplasmosis is relatively common in adults with AIDS but uncommon in children with AIDS because it is usually a reactivation of previous infection, and primary toxoplasmosis is uncommon in children.

Presentation

Clinical presentation of cerebral toxoplasmosis is variable and may include fever, focal neurological findings of recent onset, generalized or focal seizures, or subtle cognitive changes. Radiographic imaging of the brain usually reveals one or more ring enhancing mass lesions. Although these lesions are characteristic of toxoplasmosis, they are not pathognomonic.

Diagnosis

Recommendations: If *Toxoplasma* serology is positive, (Only in a child with low CD4 count and symptoms and signs compatible with cerebral toxo; NOT in a well child on or off ART with good CD4 count) a child should be treated empirically with pyrimethamine/sulfadoxin for 2 weeks before considering more invasive diagnostic procedures.

If *Toxoplasma* serology is negative or if CSF EBV PCR is positive, invasive diagnostic procedures, such as a brain biopsy, should be considered to determine the diagnosis. A positive CSF EBV PCR indicates the likelihood of CNS lymphoma.

If a favorable response to empiric treatment is documented, CNS toxoplasmosis is the presumptive diagnosis. In cases in which no improvement is documented, further invasive diagnostic procedures may be indicated to exclude other opportunistic infections, brain abscess, or tumor. Toxoplasmosis serology has 90 to 95 percent sensitivity. A negative IgG serology makes toxoplasmosis unlikely but does not entirely exclude the diagnosis.

c. **Treatment**

Recommendation: Toxoplasma encephalitis should be treated with one of the regimens listed in Table 2.5.3 for 4 to 6 weeks. Neurosurgical consultation for re-evaluation of toxoplasmosis should be obtained when the patient fails to improve with empiric therapy and further invasive diagnostic procedures are contemplated. As the risk of relapse is quite high, treatment for toxoplasmosis is usually maintained for life (Table 2.5.3).

As the risk of relapse is quite high, treatment is usually maintained for life. However, no relapse was found in adults not receiving antitoxoplasmosis prophylaxis who had immune function restoration as a result of HAART.[17] Discontinuation of treatment may be considered in adolescent patients whose signs and symptoms of toxoplasmosis have resolved and who have a sustained (>6 months) increase in their CD4 counts following HAART.

Table 2.5.3: Standard and alternative drug regimens for treatment of toxoplasmosis

Standard regimen
Sulfadiazine 120-200 mg/kg/day divided into four doses and Pyrimethamine [loading dosage of 2 mg/kg per day (max, 100 mg) divided into two doses for 3 days, followed by maintenance dosage of 1 mg/kg per day (max, 25 mg), delivered orally]. and Folinic acid (1 to 2 mg per day in infants and 5 to 10 mg every 3 days in older children, delivered orally) for patients receiving pyrimethamine
Alternative regimen*
Clindamycin (40 to 60 mg/kg/day IV divided into 4 doses) plus pyrimethamine plus folinic acid

* The effectiveness of the alternative regimen is unproven in pediatric patients. Acceptable reasons for using the alternative regimen are patient participation in a research protocol and patient's inability to tolerate or failure to respond to the standard therapeutic regimen.

Laboratory Monitoring

Recommendation: Close monitoring of patients receiving treatment for toxoplasmosis, including CBC and serum liver enzymes, is required to detect adverse drug reactions.

Herpes Viruses

Herpes simplex virus (HSV), Varicella zoster virus (VZV), and Cytomegalovirus (CMV) are all fairly common causes of nervous system disease in children with HIV. Although all three may present with encephalitis, each has other characteristic presentations. PCR of CSF may be used to diagnose HSV, VZV, or CMV infection of the CNS. This methodology may also be helpful in determining the severity of the involvement and the efficacy of treatment. When PCR is not available, viral culture can be used, although, in the case of CMV, it may not be particularly expedient. Pathognomonic lesions can help establish a diagnosis.[18]

a. Herpes Simplex Virus

Presentation

Herpes simplex virus (HSV) can cause encephalitis, most commonly in neonates. Herpes encephalitis can occur with or without the common Skin, Eyes, and Mouth (SEM) manifestations. Neonatal herpes infections, if untreated, have a high mortality rate and commonly lead to long-term neurological sequelae.

After the neonatal period, HSV encephalitis can occur with primary or secondary infection. Alterations in personality and consciousness, convulsions, and focal neurologic dysfunction can be the presenting signs, and the course is often fulminant and rapidly fatal.

Diagnosis

Pleocytosis is common, with both lymphocytes and erythrocytes present in the CSF. Radiographic imaging and electroencephalogram (EEG) are often helpful in localizing lesions in HSV encephalitis.

Treatment

Recommendation: HSV encephalitis should be treated with acyclovir. Beyond the neonatal period, the dosage is 30 mg/kg/day IV divided into three doses administered every 8 hours for 14 to 21 days. The neonatal dose is 60 mg/kg/day IV divided into three doses administered every 8 hours for 14 to 21 days.

b. Varicella Zoster Virus

Presentation

Varicella zoster virus CNS complications may be acute or recurrent. Encephalomyelitis, dermatomal radiculo pathies associated with shingles, zoster ophthalmicus with retinal necrosis, and cranial nerve abnormalities are reported to be associated with VZV in patients with advanced AIDS. In adults, 70 percent of cases of neurological complications have shingles and/or acute retinal necrosis.

Diagnosis

Examination of CSF shows prominent pleocytosis (mean CSF white blood cell count, 126 cells/mm^3) with elevated protein (mean CSF protein, 2.3 g/L). Diagnosis is increasingly made by CSF PCR rather than by culture or tissue examination. CSF PCR is invaluable in diagnosing CNS herpes virus infection, with sensitivity ranging from 70 to 90 percent and specificity >90 percent. Radiographic imaging and EEG are often helpful in localizing lesions in varicella encephalitis.

Treatment

Recommendation: Acyclovir at 1500 mg/m^2/day IV divided into three doses administered every 8 hours for 7 to 10 days (or 30 mg/kg/day divided q8h) should be used to treat VZV infection.

c. Cytomegalovirus

Presentation

Although HAART has notably decreased the incidence of CMV disease, CMV infections are common and severe complications of HIV infection. The virus often involves the nervous system, causing retinitis, encephalitis, polyradiculoneuropathy and cranial or peripheral neuropathies.

CMV retinitis is a leading cause of blindness in persons with AIDS. Symptoms such as loss of visual acuity, blurred vision, and visual field defects may be particularly difficult to detect in children. Ophthalmologic examination usually shows characteristic retinal lesions.

CMV meningoencephalitis may present with seizures, focal findings, and altered mental status. MRI reveals foci of demyelination that are similar to that seen in primary HIV encephalopathy.

In the pre-HAART era, numerous patients with rapid progression of delirium and dementia had CMV neurological disease detected on autopsy. CMV polyradiculopathy may present with an ascending weakness. Clinical signs and symptoms are often overlooked in a very sick, nonverbal child.

Treatment

Recommendations: CMV infection may be treated with intravenous Ganciclovir (10 mg/kg per day divided into two doses every 12 hours), and maintenance therapy is needed until immune restoration occurs. For Ganciclovir-resistant retinitis, Foscarnet should be

used (limited data in pediatrics). Routine retinal examinations should be performed every 6 months in children with severe immunosuppression. CMV is susceptible to various antivirals, including ganciclovir, Foscarnet, and Cidofovir.

However, CMV infections of the nervous system, particularly encephalitis, respond poorly to standard treatments. The combination of ganciclovir plus foscarnet is currently under evaluation in clinical trials.

JC Virus

Progressive multifocal leukoencephalopathy (PML) is a chronic demyelinating disorder that results from infection with JC virus, which is a papova virus. It occurs in approximately 4 to 6 percent of adults with AIDS but is exceedingly rare in children.

Presentation

PML manifests with dementia and focal abnormalities. Lesions are commonly located in the parieto-occipital or frontal region, affecting both periventricular and subcortical white matter but may occur anywhere in the brain.[19]

Diagnosis

On MRI, images appear as areas of increased signal without mass effect on T2. Lesions rarely enhance with contrast and may be difficult to distinguish radiographically from HIV demyelination. CSF PCR for JC virus is highly sensitive in diagnosing PML. Quantitative levels in CSF may be of prognostic value, with lower levels associated with longer survival.[20]

Treatment

■ **Recommendation:** Clinicians should recommend HAART for patients with PML. In the pre-HAART era, PML had a poor prognosis. Approximately 90 percent of adults with PML died within 10 months; mean survival was 4 months. There are now a number of anecdotal reports of increased survival in patients with PML who are receiving HAART.

Progression of PML may stabilize and even revert radiographically with HAART. Specific anti-JC virus therapy has been unsuccessful, even if given intrathecally.[21]

Bacterial Meningitis

Presentation

Various bacteria may cause meningitis in HIV infected children. These patients may have nuchal rigidity, fever, headache, and focal or generalized signs of neurologic dysfunction. The encapsulated organisms, Streptococcus pneumoniae and Hemo-philus influenzae type b, are of special importance in causing such CNS infections.

Diagnosis

■ **Recommendation:** Definitive diagnosis of bacterial meningitis is made by isolating and identifying the organism from CSF or blood culture. Lumbar puncture is needed to make a correct diagnosis. A presumptive diagnosis can only be made in cases in which the patient has a consistent clinical presentation and the patient is awaiting lumbar puncture or lumbar puncture is contraindicated.

Treatment

■ **Recommendation:** Antimicrobial therapy directed at the most common etiological agents (i.e. *S. pneumoniae, H influenzae*) should be used to treat bacterial meningitis. Both vancomycin and ceftriaxone at meningitic doses should be used in the empiric treatment of community-acquired bacterial meningitis. Antibiotic choice may be modified once an organism is identified and antimicrobial sensitivities are available. Duration of therapy is usually 10 to 14 days.

Corticosteroids may be used in conjunction with antibiotics for initial therapy of *H influenzae* type b meningitis. Some authorities believe that corticosteroids have a beneficial effect on prevention of hearing loss in patients with *H influenzae* type b meningitis. The benefit of steroid use in meningitis caused by other organisms is unproven.

Clinical and Laboratory Monitoring

■ **Recommendations:** Neurologic status of patients with bacterial meningitis should be monitored daily. If diagnosis is in doubt, lumbar puncture should be repeated to diagnose bacterial meningitis and to document sterility. Hearing tests (audiogram, auditory evoked responses) should be performed in patients with bacterial meningitis before discharge and at 6-month follow up visit after discharge. Patients with bacterial meningitis may be discharged from the hospital when neurologic status is stable and adequate arrangements have been made for follow-up.

Syphilis

Presentation

The course of *T pallidum* infection may be altered by HIV infection. Pediatric patients either present with infection acquired perinatally (congenital syphilis) or with new acquisition of infection. Adolescent patients may present with the typical manifestations noted in adults. Clinical symptoms are protean.

Diagnosis

Recommendations: Neurosyphilis should be considered in the differential diagnosis of neurologic dysfunction in an HIV infected patient, regardless of serologic evidence. Definitive diagnosis can be made by positive nontreponemal (VDRL, RPR) and fluorescent treponemal antibody-absorption (FTA-ABS) tests; however, a VDRL may be negative if the infection is early. The organism may be identified by dark-field microscopy from lesions. A CSF examination (opening pressure, cell count, total protein, glucose, and VDRL) is strongly recommended for all children and adolescents co-infected with HIV and syphilis. Clinicians should perform a CSF examination in all infants with congenital syphilis born to mothers with HIV coinfection. Diagnosis is usually established by serological diagnosis (nontreponemal and treponemal tests) or by identification of the organism by dark-field microscopy. In the adult population, cases of *T pallidum* infection have been reported even when the results of these tests were negative. The frequency of this rare occurrence is not known.

A presumptive diagnosis can be made when clinical presentations are consistent with congenital syphilis, primary syphilis (genital, oral, or rectal chancres), secondary syphilis (characteristic rash), or neurosyphilis (may or may not be symptomatic). CSF may or may not have pleocytosis, high protein, and a positive non-treponemal test (VDRL). When neurosyphilis is suspected, a CSF examination is required. Pleocytosis, high protein, and a positive nontreponemal test may or may not be present. If these findings are present, the diagnosis is more secure.

Treatment

Recommendation: Treatment of syphilis should be guided by the following factors:

1. the stage of syphilis
2. whether it is congenital
3. whether it is neurosyphilis
4. whether the patient is pregnant. For specific treatment and monitoring recommendations for syphilis, clinicians should refer to the Centers for Disease Control and Prevention's guidelines (http://www.cdc.gov/std/treatment/).[22]

Mycobacteria

Mycobacterium tuberculosis (MTB) and atypical Mycobacteria may cause CNS infection.

Presentation

Patients may present with granulomatous meningitis, occasionally accompanied by progressive cranial neuropathies, or with focal clinical signs resulting from mass lesions (i.e. tuberculoma).

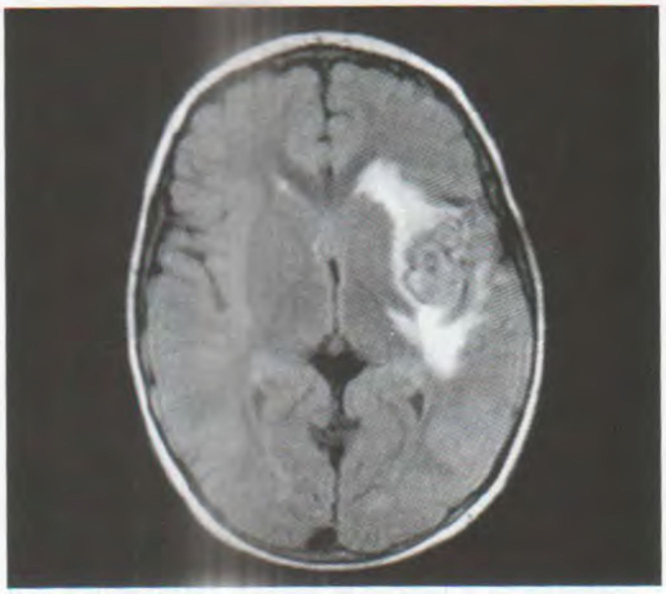


Fig 2.5.3: Tubercular granulomas

Diagnosis

Recommendations: A presumptive diagnosis should be made if the patient presents with consistent clinical findings and has a positive purified protein derivative (PPD) test. Patients with HIV and severe immune suppression may be anergic.

Because AFB smear and culture of the CSF are not very sensitive diagnostic tools, a strong effort should be made to obtain as much as 10 mL of CSF to increase the yield. CT scan or MRI with contrast will demonstrate mass lesions (Fig. 2.5.3); severe basilar meningitis may show subarachnoid enhancement at the base of the brain. Lumbar puncture may reveal high protein, low glucose, and lymphocytic pleocytosis. PCR for identification of Mycobacteria in the CSF is being studied. Definitive diagnosis of mass lesions can only be made by tissue diagnosis.

Treatment

Recommendation: Treatment of MTB CNS infection should begin immediately upon recognition of a positive smear or if other causes of meningitis are unlikely. Culture may be negative or may take several weeks to grow, and treatment should not be delayed. Symptomatic Tuberculous meningitis is invariably due to MTB. In advanced HIV disease, *Mycobacterium avium* complex is a common neuropathological finding but has little, if any, clinical impact. Suspected mycobacterium meningitis is due to MTB, unless proven otherwise.

Primary CNS Lymphoma

Primary CNS lymphoma is the most common cause of focal neurologic deficit in HIV infected children with HIV infection, accounting for approximately 4 to 6 percent of focal, mass lesions in autopsy series.

Presentation

Primary CNS lymphoma in AIDS is always of a high-grade B-cell type. Common changes in mental status include confusion, lethargy, and memory loss. Seizures are reported in approximately one-third of patients. Increased intracranial pressure may occur as a late effect.

Diagnosis

Recommendations: CNS lymphoma should be suspected in the presence of focal neurologic deficits, seizures, or changes in mental status and when the CT scan or MRI reveals a mass lesion. Children with lymphoma detected outside the CNS should be vigorously assessed for possible intracranial involvement. Lumbar puncture for Epstein-Barr virus PCR and cytology (assuming no evidence of mass effect on neuroimaging studies), and functional neuroimaging (SPECT scan) are noninvasive methods by which to diagnose lymphoma. A pediatric oncologist should be consulted. In HIV infected children, a brain biopsy may be necessary to confirm diagnosis of lymphoma.

On a CT scan, CNS lymphoma lesions appear isodense or hypodense with ill defined borders and scant edema. They are enhanced homogeneously with contrast.[23] Such masses show a high signal on dual echo (T2) MRI and are enhanced with gadolinium. Lymphoma lesions are often multifocal and may be ring-enhancing, making it difficult to differentiate both clinically and radiographically from *Toxoplasma* brain abscess. Neurocysticercosis may also present with ring-enhancing lesions and should be considered in the differential diagnosis when the patient has recently been in a country where the parasite is endemic (e.g. Mexico), or when the patient's immune function makes CNS lymphoma or toxoplasmosis unlikely.

Noninvasive methods by which to diagnose lymphoma include Epstein-Barr virus PCR and functional neuroimaging. Identification of Epstein-Barr virus in CSF by nested DNA-PCR is a sensitive (80%) and highly specific (97%) method by which to diagnose B-cell CNS lymphoma in patients with AIDS. CSF PCR assays for toxoplasmosis may also provide important information in the evaluation of CNS mass lesions. Functional neuroimaging capitalizes on differences in vascularity between lymphoma and toxoplasmosis to enhance diagnostic accuracy over conventional neuroimaging (MRI). CNS lymphoma lesions are highly vascular, resulting in focal increases in cerebral blood flow on single-photon emission computed tomography (SPECT), whereas the opposite is found with toxoplasmosis brain abscesses, which have necrotic centers and low vascularity. In adult patients with AIDS, the four-fold greater frequency of toxoplasmosis compared with lymphoma often merits empirical treatment with anti-*Toxoplasma* agents for 2 weeks. The absence of a response to treatment would then warrant performing a diagnostic brain biopsy. In children, the infrequency of toxoplasmosis argues against empirical treatment for toxoplasmosis; diagnosis usually requires a brain biopsy, especially if the child is young and *Toxoplasma* serology is negative.

Treatment

Recommendation: CNS irradiation and oral prednisone are treatments for lymphoma and may prolong survival. Success of treatment for lymphoma is disappointing, and, despite intervention, prognosis is poor; however, HAART has seemed to improve the prognosis in several cases.

HIV Related Neuropathy/Myopathy/ Myelopathy

HIV Polyneuropathy

Peripheral nerve involvement in HIV infected children can be of several types and may occur in as many as one third of HIV infected children.[23] The more common type is a sensory distal neuropathy, which usually occurs in older children with advanced HIV disease.[24,25]

Presentation

HIV related acute inflammatory demyelinating polyneuropathy is relatively rare in perinatally infected children. The clinical presentation is the same as that seen with Guillain-Barré syndrome.

Diagnosis

Recommendation: Clinical evaluation for HIV polyneuropathy (presumed to be unrelated to ARV therapy) should include an electromyogram, nerve conduction studies, lumbar puncture, and, depending on severity and type of neuropathy, a nerve biopsy. Sensory distal neuropathy is indistinguishable from the sensory neuropathy seen as a side effect of ARV treatment with Didanosine, Zalcitabine, or Stavudine. Because of lower doses of Didanosine (90 to150 mg/m^2 q12h) used in current regimens, the infrequent use of

Zalcitabine, and the less frequent occurrence with Stavudine, most sensory neuropathies are currently due to advanced HIV disease rather than to ARV exposure.[26] Nerve conduction tests may be normal with isolated sensory neuropathies. Demyelinating neuropathies typically result in elevated protein without pleocytosis, but CSF may be normal early in the course of the illness.

Treatment

Recommendation: When warranted, treatment of demyelinating polyneuropathies is the same as that for inflammatory demyelinating polyneuropathies. Treatment should be given in consultation with a neurologist. Plasmapheresis and intravenous immunoglobulin are both efficacious for treating acute demyelinating polyneuropathies. HIV related neuropathy may improve with heightened control of HIV replication. Neuropathic pain may respond to palliative treatment with Gabapentin, Carbamazepine, or Amitriptyline.

HIV Myopathy

Inflammatory Myopathy (polymyositis) is rare in HIV infected children. In adults, toxic mitochondrial Myopathy induced by NRTIs has been described, related to duration but not to dosage of zidovudine.[27] It usually accompanies an inflammatory Myopathy.

Presentation

Clinical findings include proximal muscle weakness, myalgias, and increase in serum creatine kinase.

Diagnosis

Recommendation: Diagnosis of HIV Myopathy is made by clinical observations and evidence of myopathic changes on electromyogram. Mitochondrial Myopathy can be diagnosed by muscle biopsy and respiratory chain assays.

Treatment

Recommendation: Discontinuation of a specific NRTI and its replacement with another ARV agent should be considered in patients with Myopathy. Prednisone should be considered in patients with Myopathy.

HIV Myelopathy (Fig. 2.5.4)

Spinal cord involvement is commonly noted in autopsies of adults with HIV infection but is rare among children with HIV infection.

Presentation

Spinal cord pathology of affected children may show demyelinating changes of the corticospinal tracts and vacuolar changes or myelitis attributable to HIV-1 or other viruses (e.g. cytomegalovirus).[24]

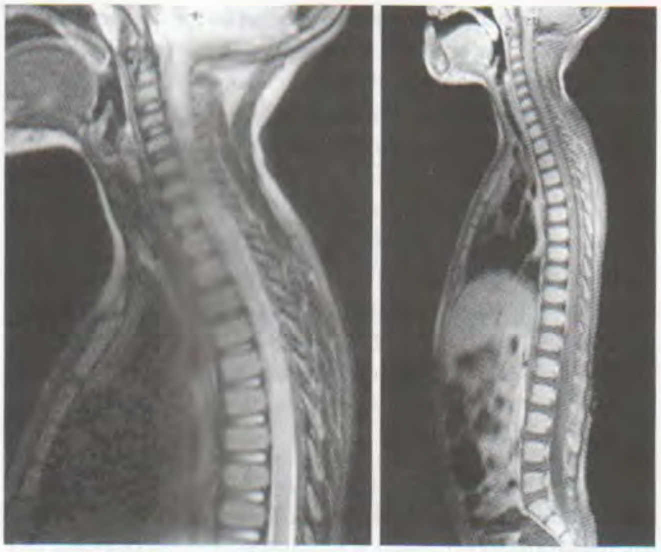


Fig. 2.5.4: HIV myelopathy (pre ARV and post ARV)

Diagnosis

Recommendations: HIV myelopathy should be suspected in an HIV infected child when spastic paraparesis (bilateral lower extremity hypertonia) without cognitive decline is the predominant neurological finding.

MRI of the brain should be performed to exclude bilateral cerebral involvement mimicking spinal compromise. Magnetic resonance of the spine is usually normal but occasionally may show high signal intensity on T2 consistent with demyelination. Abnormalities in CSF, when present, are nonspecific. Myelopathy may be suspected clinically, but definitive diagnosis cannot be made without a brain biopsy, which is rarely performed in the absence of specific additional treatment options.

Treatment

HIV myelopathy should be treated with the same ARV agents used to treat symptomatic HIV disease, with the goal of achieving low to undetectable viral load levels on PCR testing and reversal of immune suppression. Arrest of HIV myelopathy and gradual resolution of the neurological signs and symptoms are usually achieved with effective response to HAART (decreased viral load and immune function restoration).

Seizures

Recommendations: As in non-HIV infected children, electroencephalogram testing, in addition to an MRI

scan and lumbar puncture, should be performed if indicated in the setting of seizures. Simple febrile seizures (single, brief, generalized tonic-clonic seizure) with a clear source of infection do not warrant a lumbar puncture or electroencephalogram. A lumbar puncture to exclude meningitis or encephalitis should be performed in children with complex febrile seizures, or when there is any question about their mental status, neurological examination, or source of infection. Patients with unprovoked afebrile seizures should be referred to a neurologist for seizure management.

Stroke

HIV infection produces inflammation of cerebral vessels, thereby increasing risk of stroke. In HIV infected children, the incidence of clinically overt strokes in one pre-HAART autopsy series was approximately 1.3 percent per year.[28] More than 50 percent of strokes were hemorrhagic and occurred in patients with thrombocytopenia (especially immune thrombocytopenic purpura) and CNS neoplasia. Currently, strokes are more frequently seen among children with advanced HIV disease or HIV encephalopathy. Non-hemorrhagic strokes and subarachnoid hemorrhage (SAH) were associated with arteriopathy affecting the large vessels of the circle of Willis or the medium to large meningocerebral arteries.[29]

Presentation

Clinical signs in patients experiencing stroke include focal clinical signs, seizures, and changes in mental status. HIV related strokes may be clinically silent, especially among children with advanced HIV encephalopathy.

Diagnosis

Recommendations: Strokes should be suspected with the onset of focal clinical signs, seizures, or changes in mental status. When a patient presents with these signs and symptoms, the clinician should consult with a pediatric neurologist. MRI with diffusion weighted imaging is the most sensitive imaging technique available to identify strokes. An angiogram or angio-MRI may assist in determining the extent of vascular compromise. Possible cause(s) for stroke (e.g. coagulopathy, neoplasia) should be identified, as well as whether the stroke is hemorrhagic or ischemic. If subarachnoid hemorrhage occurs without obvious precipitating factors (i.e. trauma, neoplasia, coagulopathy), the rupture of an aneurysm should be suspected and imaging tests should be obtained (MRA, angiogram). A neurosurgical consult should be obtained if intraparenchymal hemorrhage, especially with mass effect, or an aneurysm is found.

Hemorrhage is easily identified on a CT scan; however, in cases of ischemic, non-hemorrhagic (bland) strokes, CT images may be normal in the first 24 hours and may need to be repeated. The CT scan should be followed by an MRI with diffusion weighted imaging, which, if negative, excludes cerebral infarction.

Treatment

Recommendations: Subarachnoid hemorrhage should be managed by the consulting neurologist and neurosurgeon. There is no specific drug treatment for HIV related ischemic strokes. A rehabilitation medicine specialist should be consulted early in the course of a stroke. All patients with subarachnoid hemorrhage should be monitored in intensive care, and neurological examination should be performed frequently with attention directed to changes in mental status. Increased intracranial pressure should be treated as necessary.

Key Messages

- Central nervous system (CNS) abnormalities may result from direct invasion of the CNS by HIV or by indirect effects of the virus on the CNS.
- Patients with HIV who are severely immunosuppressed may develop opportunistic CNS infections.
- Children with HIV are at increased risk of developing focal CNS neoplasms such as lymphoma.
- Psychiatric manifestations of HIV infection may occur in children.
- In HIV, CNS involvement is more common in children than adults.
- HIV Infection should be suspected in children presenting with unexplained neurological manifestation and growth failure .
- The Involvement of other organ system is variable and CNS involvement may be the solitary manifestation of HIV Infection.
- Risk of HIV encephalopathy depends upon CD4 count and load of virus in CSF.
- The use of HAART is highly effective in reducing the incidence of HIV encephalopathy among perinatally infected children and effective CNS penetrating antiretroviral regimen is also important in survival after diagnosis of HIV encephalopathy.

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2.6

Pulmonary Manifestations in Children with HIV

Mamatha M Lala, Rashid H Merchant

Introduction

Pulmonary diseases continue to cause significant morbidity and mortality in Human Immunodeficiency Virus (HIV) infected children despite availability of advanced effective treatment. Infection remains the most prevalent cause of death for HIV infected younger children with a significant number of them being pulmonary infections. However, this frequency tends to decrease with increasing age.

Common pulmonary diseases seen in HIV infected children are (Table 2.6.1):

1. Opportunistic infections due to bacterial, viral and fungal pathogens.
2. Lymphoproliferative processes like lymphoid interstitial pneumonias (LIP), immune reconstitution inflammatory syndrome (IRIS), pulmonary lymphoid hyperplasia (PLH), lymphoproliferative thymic cysts.
3. Conventional infectious processes that may be exacerbated by the immune deficiency caused by HIV infection *per se*.
4. Disorders like asthma/reactive airway disease.
5. Others: Bronchiectasis, spontaneous pneumothorax, pulmonary symptoms associated with neoplastic, toxic, cardiac disease, etc.

Table 2.6.1: Causes of lung diseases seen in HIV infected children

Opportunistic infections
Bacteria
• *Mycobacterium tuberculosis*
• *Streptococcus pneumoniae*
• *Haemophilus influenzae*
• *Staphylococcus aureus*
• *Pseudomonas aeruginosa*
• *Klebsiella pneumoniae*
• *Atypical mycobacteria*
Contd...
Contd...
Fungi
• *Pneumocystis jerovicii (PCP)*
• *Cryptococcus neoformans*
• *Histoplasma capsulatum*
• *Coccidioides immitis*
• *Penicillium marneffei*
Viruses
• *Cytomegalovirus (CMV)*
• *Epstein-Barr Virus (EBV)*
• *Herpes Simplex Virus (HSV)*
• *Varicella Zoster Virus (VZV)*
Protozoa
• *Toxoplasma gondii*
• *Strongyloides stercoralis*
Neoplasms
• *Lymphoma*
• *Tumors of smooth muscle origin*
• *Mucosa associated lymphoid tissue lesions (MALT)*
• *Pulmonary Kaposi sarcoma*
Others
• *Upper Respiratory Tract Illnesses- URTI, sinusitis, otitis media, Bronchitis, pertusis, LIP (Lyphoid Interstitial Pneumonia)*
• *Asthma*
• *Bronchiectasis*
• *Immune Reconstitution Inflammatory Syndrome (IRIS)*
• *Spontaneous pneumothorax*
• *Foreign body aspiration*
• *Severe gastroesophageal reflux*
• *Metabolic derangement - systemic acidosis, PLH (Pulmonary Lymphoid Hyperplasia)*
• *Lymphoproliferative thymic cysts*
• *Pulmonary symptoms associated with cardiac disease—Congestive cardiac failure, Cardiomyopathy, Cardiomyopathy secondary to Zidovudine exposure*
• *Cystic fibrosis*
• *Alveolar hemorrhage*
• *Sarcoid*

Pneumocystis jerovecii Pneumonia (PCP) is considered to be the most common pulmonary complication of pediatric HIV infection in the developed world. In contrast, pulmonary tuberculosis far exceeds recurrent bacterial pneumonias, PCP or LIP as the primary pulmonary complication of pediatric HIV infection in

countries where tuberculosis (TB) is endemic and poses as a major cause of morbidity and mortality. Many of these infections involve the lower respiratory tract either as a primary site of infection or as one of the sites involved in disseminated disease. The development of chronic lung disease is common in HIV infected children and may result from recurrent or persistent pneumonia due to bacterial, mycobacterial, viral, fungal or mixed infections. Neoplastic pulmonary diseases common in the adult AIDS population are rare in the pediatric patient. Diagnosis and management is often difficult in the resource limited setting, especially as most HIV related pulmonary disease presents in infancy or early childhood. In the context of HIV, children are at increased risk of diagnostic errors because of overlapping clinical and radiographic features of most pulmonary diseases. Moreover, most infections require multiple drugs for prolonged periods for effective therapy and prevention of development of drug resistance, making drug to drug interactions and drug toxicities more common and treatment adherence more complicated, thereby posing as an enormous challenge to both clinicians and public health workers. Advances in our understanding of these disease processes and their clinical manifestations have allowed development of systematic approaches to the common problem of the HIV infected child with pulmonary disease. These approaches, coupled with improvements in diagnosis and available treatment options/ prophylactic strategies for the most serious pulmonary infections, especially Pneumocystis jerovecii pneumonia (PCP), as also for Mycobacterial infections, have led to earlier diagnosis and improved survival.

Epidemiology

Pulmonary disease, usually infectious, has been considered to be the most prominent manifestation of AIDS in children as well as adults and was once thought to be a universal feature of pediatric AIDS.[1,2] As per the multicentric P(2)C(2) study, pulmonary disease remained an important cause of HIV related deaths, being the underlying or contributory cause in 41.9 percent of all deaths. Chronic lung disease was present in 58.1 percent of all children who died and the role of pulmonary disease and particularly infectious pulmonary disease in mortality showed a decreasing trend with age.[3] Worldwide, tuberculosis remains the most frequent coinfection in subjects with HIV-1 infection and is a major cause of morbidity and mortality. There were 9.2 million new cases of TB in 2006, including 700,000 cases among people living with HIV, and 500,000 cases of multidrug resistant TB (MDR-TB) the highest levels ever recorded.[4] PCP is still considered to be the most common pulmonary complication of pediatric HIV infection in the developed world.[5] In contrast, pulmonary tuberculosis (PTB) far exceeds recurrent bacterial infections or PCP as the primary clinical manifestation of pediatric HIV disease in countries where TB is endemic.[6-8] LIP is the second most common pulmonary complication of pediatric HIV infection.[5] Mixed respiratory infections are a particular feature of HIV infected children.

Pulmonary Tuberculosis

Coexisting HIV infection has been the most important factor for the resurgence of TB worldwide. TB and HIV seem to be in perfect harmony with each other, each facilitating the other in multiplying rapidly, leading to early clinical progression and death. The diagnosis of childhood TB that has always been difficult and remains even more challenging in the face of the dual epidemic of HIV and TB, especially in resource limited settings.[9] TB in HIV infected children can be more severe and progression to death more rapid than in the HIV uninfected children. In many countries it is a norm to give BCG vaccination at birth, including ours, even in a perinatally HIV exposed infant as it seems to give protection against disseminated and severe forms of the disease than it does against Pulmonary TB. In the presence of coinfection, children are at increased risk of diagnostic errors because of overlapping clinical and radiographic features. Both infections require multiple drugs for prolonged periods for effective treatment and prevention of development of drug resistance, making drug-to-drug interactions and drug toxicities more common and treatment adherence more complicated. Nevertheless, the treatment of tuberculosis in the HIV infected child is critically important irrespective of antiretroviral therapy. Clinical manifestations at the time of initial infection vary according to the age of the child and immune response. In general, the clinical features and radiological manifestations in children with relatively preserved immunocompetence may be indistinguishable from that in non-HIV infected children, although the disease is usually more severe. Although, TB can occur in HIV with any level of CD4 counts, generally coinfected patients tend to have lower CD4 counts. As HIV infection progresses and immunity declines, rapidly progressive disseminated disease is seen.

The most common presenting symptoms of pulmonary primary TB are cough, fever, wheezing, decreased appetite, and fatigue. Children with pulmonary primary TB may be asymptomatic despite abnormal radiographic findings. Physical findings may be relatively mild compared with the extent of radiographic findings and may include rales, bronchial breath sounds, wheezing, decreased breath sounds, but respiratory distress is infrequent unless there is extensive disease. In primary

tuberculosis occurring as a result of recent infection, the process is generally seen as middle or lower lung zone infiltrate, often associated with ipsilateral hilar adenopathy. The primary complex named "The Ghon Complex" after Ghon who described it in 1916, consists of a relatively small area of alveolar consolidation, lymphangitis and regional lymphadenitis. Early in the course of the illness cough may be nonproductive, but subsequently, as inflammation and tissue necrosis ensue, sputum is usually produced. Inflammation of the lung parenchyma adjacent to a pleural surface may cause pleuritic pain. Segmental lesions, consolidation, atelectasis may result from compression of airways by enlarged lymph nodes. As tuberculosis progresses, infected material may spread into other parts of the lungs, causing a patchy bronchopneumonia, multilobar infiltrates and diffuse interstitial disease. Erosion of a parenchymal focus of tuberculosis into a blood or lymph vessel may lead to dissemination of the organism and a miliary lung and other disseminated forms of TB. In older children and adolescents, Pulmonary TB is generally like in adults often with pleural effusion, cavitation with sputum smear positivity. Like adults, such patients present with fever, weight loss, a productive cough, hemoptysis, and night sweats. Radiographic findings include cavitary lesions, typically in the upper lobes. Pediatric patients with TB are usually not infectious as they lack cavities with a large number of bacilli, and the relatively weak cough of young children is not conducive to the airborne transmission of organisms.

The diagnosis of childhood TB remains a problem even in the best of centers because of the paucibacillary nature of the disease and the difficulty of obtaining sufficient sputum from infants and young children for smear microscopy and culture. Obtaining early morning gastric aspirates for AFB stain and culture preferably on 3 consecutive days is the method of choice when attempting to diagnose TB in young children who are unable to produce sputum. In the presence of HIV, the diagnosis can be obscured by the frequency of atypical clinical and radiographic findings and overlap with other AIDS-associated infections, the likelihood of anergy on tuberculin testing and the increased likelihood of a negative acid-fast smear of sputum. It is easy to over diagnose as well as under diagnose this condition. The diagnosis is based on circumstantial evidence, basic components of history- signs and symptoms including previous TB or contact with infectious case, Tuberculin skin testing, radiographic findings, with or without microbiologic confirmation with smear/ culture. Culture of *M. tuberculosis* is expensive, has a low yield, and is not available in most low-income countries. In the best circumstances, the highest yields are about 40 percent. BACTEC is a radiometric assay that is quick but not superior to a conventional culture method. More recent diagnostic techniques include polymerase chain reaction (PCR), Nucleic Acid Amplification (NAA), Septi-check AFB system, Mycobacterial Growth Indicator Tube system, serology tests, and immunoassays based on detection of cellular responses to specific *M. tuberculosis* antigens.

Always look for three important clues to TB in children:

1. Contact with an adult or older child with smear-positive Pulmonary TB.
2. Failure to thrive or weight loss.
3. Respiratory symptoms such as cough lasting for more than three weeks in a child who has received a course of broad-spectrum antibiotics and not responded.

A positive tuberculin skin test (TST) reaction is the hallmark of primary infection and a reading of ≥ 5 mm is considered positive and indicative of tuberculous infection in the presence of HIV. As Cell Mediated Immunity is central to the response of TST, in HIV, cutaneous anergy leading to false negative tests becomes increasingly common as the immune defect increases. Hence, a negative result does not exclude tuberculosis. No CXR pattern is absolutely typical of PTB, especially with underlying HIV infection. Radiographic manifestations of pulmonary primary TB include intrathoracic lymphadenopathy of the hilar, mediastinal, and subcarinal nodes and parenchymal changes (Figs 2.6.1 and 2.6.2).

The parenchymal findings include segmental hyperinflation and atelectasis (Fig. 2.6.3) caused by bronchial obstruction, alveolar consolidation, interstitial densities, occasionally cavities (Fig. 2.6.4), bronchiectasis



Fig. 2.6.1: CXR PA View—Hilar lymph gland enlargement with infiltration into the surrounding lung tissue



Fig. 2.6.2: CXR PA view showing infiltrates in the periphery of the right middle zone of the lungs, with enlargement of lymph nodes in right hilum

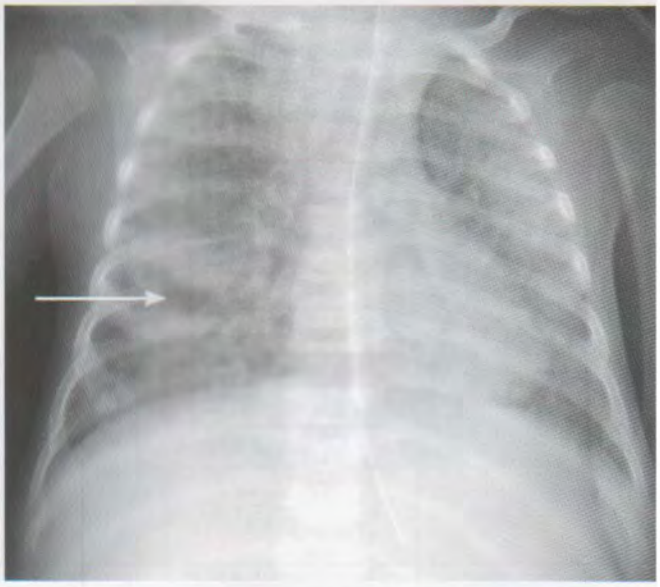


Fig. 2.6.4: CXR showing severe bilateral bronchopneumonia and a cavity in the right middle lobe (see arrow)

(Fig. 2.6.5) and miliary TB. In miliary TB chest radiographs reveal evenly distributed small, millet-sized (less than 2 mm), round opacities through out the lung fields (Fig. 2.6.6).

Therapy for TB in the HIV infected patient yields very good results, contrary to most other HIV associated opportunistic infections. Compliance is a major determinant of success of therapy. The WHO Clinical Manual on HIV/TB provides a detailed guidance on clinical management of these patients (Table 2.6.2).[10] The Center for Disease Control and prevention (CDC) recommends a minimum 9 months of Anti-TB treatment for HIV infected active pulmonary disease, and a minimum of 12 months therapy for those with miliary disease.[11] In India, Directly Observed Treatment Short Course (DOTS) has been implemented under the Revised National Tuberculosis Control Program (RNTCP). Efforts to involve the children under the purview of RNTCP have recently resulted in the development of guidelines (Table 2.6.3 and Table 2.6.4) for management of pediatric patients.[12,13] In general, the priority is to treat

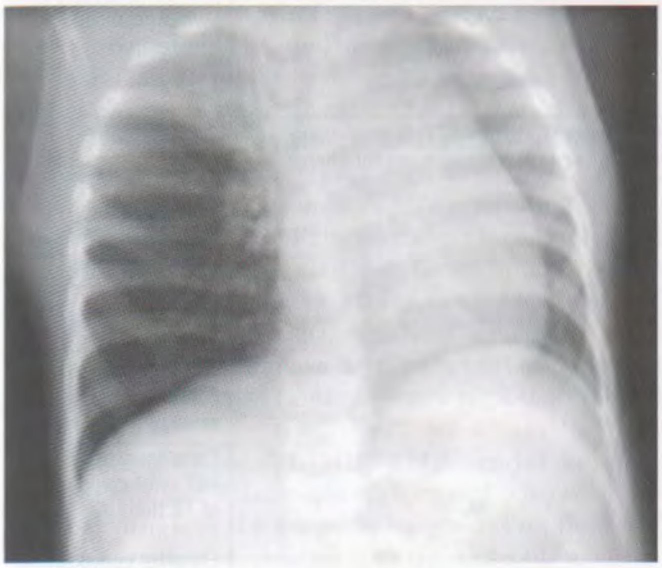


Fig. 2.6.3: CXR AP view showing segmental atelectasis of the right upper lobe with hyperinflation of right middle and lower lobe



Fig. 2.6.5: CXR showing right sided tuberculous empyema



Fig. 2.6.6: CXR PA view showing extensive bilateral miliary mottling

TB, especially smear-positive PTB to interrupt transmission. However, Antiretroviral Therapy (ART) and anti-TB treatment can be instituted, if managed carefully. If TB is detected prior to ART initiation, TB therapy is to be completed if possible before starting ART or at least delayed if possible, till the initial intensive phase of anti-TB treatment of 2 months is completed in order to avoid the development of drug-to-drug interactions, additive side effects or IRIS. For details of IRIS please see the section on IRIS given in this chapter. Rifampicin stimulates the activity of the cytochrome P450 liver enzyme system, which metabolizes Protease Inhibitors (PI) and Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI). This can lead to decreased blood levels of PIs and NNRTIs. PIs and NNRTIs can also enhance or inhibit this same enzyme system, and lead to altered blood levels of Rifampicin. The potential drug interactions may result in ineffectiveness of ARV drugs, ineffective treatment of TB or an increased risk of drug toxicity. Isoniazid can cause peripheral neuropathy. The Nucleoside Reverse Transcriptase Inhibitors (NRTI)-Didanosine, Zalcitabine and Stavudine may also cause peripheral neuropathy. There is a potential added toxicity

Table 2.6.2: WHO recommendations for HIV infected children already on ART, newly diagnosed with TB

Time of TB diagnosis in relation to ART	*Underlying cause of TB*	*Consideration for ART following initiation of TB treatment (with a rifampin-containing regimen)*	*ART regimen*
Child on standard first-line regimen (2 NRTI + 1 NNRTI) diagnosed with TB	TB due to primary infection (consider at any-time during ART, depending on exposure to TB)	Continue ART but assess for need for change in ART regimen; response to TB therapy should be used to evaluate need for change	**Preferred:** continue on standard 2 NRTI + 1 NNRTI first-line regimen of using EFV
	TB as part of immune reconstitution syndrome (consider in first 3 months of ART)		**Alternative:** switch to 2NRTI + Ritonavir if <3 years and on NVP if possible
	TB as sign of treatment failure of first-line regimen (consider only after 24 weeks of ART)		Switch to second line regimen
Child on standard Second-line regimen (NRTI/NNRTI+ bloosted PI) diagnosed with TB	TB due to primary infection (consider at anytime during) ART depending on exposure to TB)	Assess need for changing or stopping ART regimen; response to TB therapy should be used to evaluate need for change	Continue same regimen, consider adding RTV to achieve full therapeutic RTV dose (increase RTV until same dose as LPV in mg) Consider consultation with experts for construction of a salvage regimen
	TB as sign of treatment failure of second-line regimen (consider only after 24 weeks of ART)		Consider stopping ART until completion of TB therapy Consider consultation with experts for construction of a salvage regimen

Table 2.6.3: First line anti-TB drugs

Drug (abbreviation)	Mode of action	Potency	Recommended dose in children (mg/kg body weight)	
			Daily	Intermittently (3 times/week)
Isoniazid (H)	Bactericidal	High	5	10
Rifampicin (R)	Bactericidal	High	10	10
Pyrazinamide (Z)	Bactericidal	Low	25	30-35
Streptomycin (S)	Bactericidal	Low	15	15
Ethambutol (E)	Bacteriostatic	Low	15	30

Table 2.6.4: RNTCP treatment regimens

Category	Type of patient	Treatment regimen	
		Intensive phase	Continuation phase
I.	New sputum smear +ve PTB Seriously ill* smear -ve PTB Seriously ill EPTB	$2H_3R_3Z_3E_3$***	$4H_3R_3$
II.	Sputum smear +ve relapse Sputum smear +ve treatment failure	$2S_3H_3R_3Z_3E_3$/ $1H_3R_3Z_3E_3$	$5H_3R_3E_3$
III.	Sputum smear _ve and EPTB, not seriously ill**	$2H_3R_3Z_3$	$4H_3R_3$
IV.	Multidrug Resistant TB	6-9 Km Ofx Eto Cs Z E/ 18 Ofx Eto Cs E	

PTB: Pulmonary Tuberculosis
EPTB: Extrapulmonary Tuberculosis
H: Isoniazid R: Rifampicin Z: Pyrazinamide E: Ethambutol S: Streptomycin
Km: Kanamycin Ofx: Ofloxacin Eto: Ethionamide Cs: Cycloserine
* Seriously ill sputum smear -ve PTB includes all forms of PTB other than primary complex
** Not seriously ill EPTB includes lymph node TB and unilateral pleural effusion
*** Prefix indicates month and subscript indicates thrice weekly

if Isoniazid is added. Isoniazid also has a theoretical interaction with Abacavir. Frequent symptom review and blood testing should be used to monitor patients receiving both ART and Anti-TB treatment, since adverse drug reactions are more frequently observed in cotreated patients. In addition, Anti-TB treatment may result in frequent adverse interactions with other medications commonly used in the course of HIV infection. Notably, Rifampin may decrease Ketoconazole, Fluconazole, and Clarithromycin serum levels. Given the exceptionally high burden of TB in ART centres in India, a national framework of TB-HIV collaborative activities have been extended to the entire country and have been included as an integral part of National AIDS Control Program (NACP) III and RNTCP II.[14]

Multidrug resistant TB (MDR-TB) defined as resistance to Isoniazid and Rifampicin with or without resistance to other drugs, in the same time period is on the rise.[4] Drug-resistant *M. tuberculosis* is as transmissible as drug-susceptible *M. tuberculosis* and remains drug resistant in a new host. The treatment of HIV positive individuals with MDR-TB is the same as for HIV negative patients (Table 2.6.3 and 2.6.4). However treatment is more difficult and adverse events more common. Rigorous monitoring in this particular group of patients is required in order to ensure adherence to treatment, early identification and treatment of adverse events and reduce default. In general, it is recommended that patients who are already on ART at the time of MDR-TB diagnosis be continued on it when TB therapy is initiated. For patients not on ART, TB therapy should be started followed by initiation of ART within 2-4 weeks. However the potential drug interactions may result in ineffectiveness of HIV and/or TB Treatment and an increase risk of drug toxicity. Occasionally patients may develop IRIS as a result of immune restitution due to the simultaneous administration of ART and Anti TB Treatment.

For a comprehensive information on HIV and TB Coinfection in Children, kindly refer the Chapter written by the same author in "Practical Approach to Tuberculosis Management" 2006, VK Arora, Raksha Arora, First Edition, Jaypee Brothers.[15]

Infection with Mycobacteria other than Tuberculosis (MOTT)

Commonly found in the environment and referred to as Mycobacterium Avium Complex (MAC): *M. avium, M. intracellulare, M. paratuberculosis, M. lepremurium and M. scrofulaceum*, are major opportunistic pathogens resulting in systemic infection associated with severe immuno-suppression and late stage disease. Respiratory symptoms and isolated pulmonary disease is rare, although the organism may be detected in bronchoalveolar fluid (BAL).[16] Diagnosis is accomplished by isolation of organism from blood or biopsy sites (bone marrow, lymph node or other tissues). Culture can yield the organisms in 2 weeks and is necessary for species identification. Anemia out of proportion to the stage of the HIV disease and elevated serum alkaline phosphatase may be seen. With advent of ART and resulting improved preservation of immune competence, MAC infections are less common.[17] However, it remains an important cause of morbidity and mortality in advanced HIV disease and warrants effective therapeutic and prophylactic management. Effective treatment involves multidrug therapy with Clarithromycin (7.5–12.5 mg/kg/dose twice daily) or Azithromycin (5-10 mg/kg/dose once daily) with Ethambutol (15 mg/kg/dose once daily) with careful monitoring for toxicities and drug interactions. Most patients show improvement within 4-6 weeks. Treatment should then be continued with 2 drugs. MAC prophylaxis has not been evaluated in children, however based on adult studies, either Clarithromycin (7.5 mg/Kg/dose daily) or Azithromycin (20 mg/Kg/dose once weekly) is recommended depending on CD4 lymphocyte count (CD4 count<50 in >6 years, CD4 count <75 in 2-6 years, CD4 count <500 in 1-2 years, CD4 count <750 in <1 year), which can be discontinued once the child has a sustained increase of CD4 count level above threshold for >3 months. Secondary prophylaxis in a child who has suffered from MAC infection, however needs to be continued for life.

Bacterial Pneumonias

Bacterial pneumonias are very common in all HIV infected children and recurrent bacterial pneumonias are a severe manifestation of HIV disease. Bacterial pneumonias can occur at any time during the course of HIV infection and at any CD4 lymphocyte count, but the rate increases with increasing immunosuppression. One third of HIV infected children who experience acute pneumonia have recurrent episodes.[18] The commonest cause is *Streptococcus pneumoniae* and response to treatment is usually satisfactory. Other causes include *Haemophilus influenzae, Salmonella, Staphylococcus aureus, Klebsiella pneumoniae* and *Escherichia coli*. The presentation of PTB in infants can be acute, so PTB should be considered when there is a poor clinical response to standard antibiotics and the mother has TB. Pneumonia due to *Staphylococcus* or *Klebsiella* may be a problem in HIV infected children with chronic lung disease. Recurrent pneumonias can result in acute or chronic alterations in lung architecture and can cause cystic changes and cavitation including bullous lung disease and bronchiectasis. Because of difficulties obtaining appropriate specimens (e.g. sputum) from young children, bacterial pneumonia is most often a presumptive diagnosis. The diagnosis of pneumonia is most typically made on the basis of clinical features: high fever, cough, respiratory distress with or without hypoxemia and/or wheezing and radiographic findings. In patients with underlying chronic lung disease / LIP, superimposed bacterial pneumonia may significantly worsen the respiratory status. Chest radiographs usually show focal infiltrates or consolidation (Fig. 2.6.7). Sputum is extremely difficult to obtain in very small children. Sputum induction obtained by nebulization with hypertonic (5%) saline has been evaluated for diagnosis of pneumonia in 210 South African infants and children (median age: 6 months), 66 percent of whom had HIV infection.[19] The procedure was well tolerated, and identified an etiology in 63 percent of children with pneumonia (identification of bacteria in 101 children, *M. tuberculosis* in 19 children, and PCP in 12 children). Culture of blood and pleural fluid, if present, should be done. Assays for detection of bacterial antigens or evidence by molecular biology techniques are important for the diagnostic evaluation of HIV infected children in whom unusual pathogens might be involved or difficult to identify or culture by standard techniques. The local prevalence of resistance to common

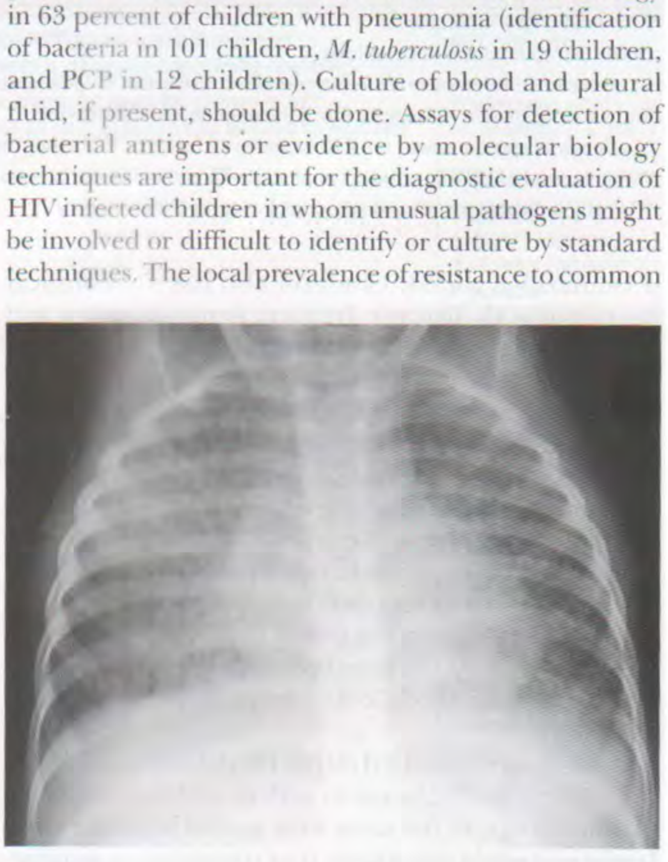


Fig. 2.6.7: LIP. Note the coarse nodules of varying sizes. Compare this picture to the typical miliary TB picture in Figure 2.6.6

infectious agents (i.e. penicillin-resistant *S. pneumoniae* and methicillin-resistant *S. aureus*) and the recent use of prophylactic or therapeutic antibiotics should be considered when initiating empiric therapy. The first choice if the condition of the patient is not severe is Amoxycillin or Cotrimoxazole. In patients on cotrimoxazole prophylaxis, the use of cotrimoxazole to treat bacterial respiratory infections is not indicated. An alternative is Amoxy-Clavulanic acid or second-generation Cephalosporins (cefuroxime, cefaclor). Seriously ill patients with a respiratory infection should receive a combination with Chloramphenicol or Ceftriaxone to cover for Gram-negative infections. Treatment for severe life-threatening pneumonia could be: Ceftriaxone + Amikacin (*Gram-negatives + Gram-positives, also staphylococcus*), or chloramphenicol + cloxacillin (*Gram-negatives + Gram-positives, including staphylococcus, atypical bacteria -chlamydia, mycoplasma*). When the organism is identified, antibiotic susceptibility testing should be performed and therapy based on the results of susceptibility testing. HIV infected children whose immune systems are not seriously compromised and who are not neutropenic can be expected to respond similarly to HIV uninfected children and should be treated with the usual antimicrobial agents recommended for the most likely bacterial organisms. The incidence of invasive *pneumococcal* disease and *Hemophilus influenzae* disease can be decreased among HIV infected children with effective vaccination and hence prophylactic vaccines against these bacterial pathogens is recommended in HIV positive children.[11]

Pneumocystis Jerovecii Pneumonia

Pneumocystis jerovecii (formerly known as *carinii*) pneumonia (PCP) is the most common AIDS defining condition and most life-threatening opportunistic infection in children with HIV in developed countries.[5] Serum antibodies to the organism is said to be present in large number of children by 2-4 years of age, suggesting that primary asymptomatic infection occurs in immuno competent hosts.[20] Since the time of the AIDS epidemic, patients most at risk remain those with advanced HIV infection with impaired cell mediated immunity. The incidence has however dramatically decreased with the use of ART and routine use of prophylaxis. The highest incidence of PCP in HIV infected children is the first year of life, with cases peaking at age 3–6 months and at a much higher CD4 cell counts than older children or adults. Therefore, all HIV exposed infants should receive prophylaxis for PCP from the age of 6 weeks for the first year of life or until lack of HIV infection is documented[11] as per the publication of the 1995 PCP prophylaxis guidelines, which remains the same to date. Also, Primary prophylaxis with cotrimoxazole [dose of 5 mg/kg/day (Trimethoprim component) as a single daily dose] is a standard component of HIV care in children less than five years of age. For children older than 6 years of age, the CD4+ cell count predicts disease in a manner similar to adults and CD4 cell counts <200 cells/c.mm are considered an indication for prophylaxis.

PCP usually presents as an acute, severe pneumonia in infants less than 6 months of age and in children it is similar to that in adults with fever, tachypnea, dyspnea, cough, usually nonproductive. The severity of these signs and symptoms might vary from child-to-child and the onset can be abrupt or insidious with nonspecific symptoms developing over a period of weeks - mild cough, lethargy, chest pain, poor feeding, and weight loss. Some may not have fever, but almost all patients will have tachypnea. Physical examination might show respiratory distress with bibasilar rales with evidence of respiratory distress and hypoxia. Hypoxia is a prominent feature and may be less responsive to oxygen unlike other bacterial pneumonias. Lactic dehydrogenase (LDH) is often increased but is not specific for PCP.

The commonest radiographic abnormalities are diffuse bilateral interstitial infiltration with a ground glass or reticulogranular appearance and hyperinflation.Hilar adenopathy may also be present, though rare. May be normal at times, or have multiple pulmonary cysts and cavities resulting from lung destruction and necrosis, nodular or miliary lesions, pneumothorax, or pneumomediastinum. High resolution CT has increased sensitivity and specificity over chest radiographs and may reveal abnormalities despite a normal chest radiograph. The differential diagnoses include bacterial, viral, fungal pneumonias, PTB, LIP. The definitive diagnosis of PCP rests on histopathalogical demonstration of organisms/ cysts in induced sputum, bronchoalveolar lavage or biopsy specimens which require special stains. Molecular diagnosis using polymerase chain reaction (PCR) assays in blood or serum, nasopharyngeal aspirates, and bronchoalveolar lavage specimens are more for research purposes. These investigations are often not possible in resource limited settings. The diagnosis therefore is often empirical and depends on the clinical and radiological features, exclusion of TB and response to a trial of high-dose cotrimoxazole which should be instituted without delay, combined with corticosteroids if there is severe dyspnea.

Trimethoprim / Sulfamethoxazole (TMP/SMX) is the recommended treatment for PCP in the dose of 20 mg/kg body weight /day of the TMP component (100 mg/kg of SMX component) administered intravenously as an infusion over an hour, in 3-4 divided doses for 21 days. However due to unavailability of the injectable preparation or high cost in resourse limited settings, oral treatment with

the same dose can be given and is generally effective. If the patient does not improve within 4-7 days other etiologies must be pursued, treatment failure should be considered and alternate therapy may be warranted. Coinfection with other organisms like pneumococcus, CMV, may be present in HIV infected children giving rise to more severe disease. Adverse reactions to TMP/SMX include rash (including erythema multiforme and rarely Stevens Johnson syndrome), hematologic abnormalities (e.g. neutropenia, thrombocytopenia, megaloblastic, or aplastic anemia), gastrointestinal complaints (usually mild), hepatitis, and renal disorders (e.g. interstitial nephritis). Dapsone/Trimethoprim, Pentamidine, Atovoquone, Primaquin, Clindamycin, Trimetrexate glucuronate with folinic acid are some of the alternate drugs. A short course of corticosteroids tapered gradually over weeks might be indicated in some severe cases with severe hypoxemia and respiratory failure. Surfactant therapy may offer a possible treatment strategy for desperately ill infants as patients with PCP may have decreased amount of surfactant. Lifelong suppression in prophylactic doses is indicated following treatment for PCP to prevent recurrence. Safety of discontinuation of secondary prophylaxis after immune reconstitution with ART in children has not been studied extensively.

Viral and Fungal Pneumonias

The viruses which cause lower respiratory tract infections in immunocompetent children also infect children with HIV infection – *Respiratory Syncytial virus (RSV), para influenza viruses, influenza viruses, adenoviruses*, etc. They may cause primary pneumonia or worsen a pre-existing/concurrent opportunistic infection. They may cause potential systemic involvement and prolonged viral excretion. Chronic interstitial pneumonitis due to *Cytomegalovirus (CMV) or Varicella* pneumonitis are uncommon in children. CMV pneumonia is generally interstitial in nature with gradual onset of shortness of breath and a dry non-productive cough with minimal auscultatory findings. Usually there is other end organ CMV disease with profound immunosuppression and the prognosis is very poor with high early mortality and a median survival after diagnosis of <30 days.[21] Although the exact incidence of fungal pneumonia is unknown, pulmonary mycosis is being increasingly encountered in HIV infected children as a consequence of severe immunodeficiency.[22] *Histoplasmosis, candidiasis, penicilliosis, cryptococcosis, coccidiodomycosis and nocardiosis* may all present with pulmonary involvement with progressive pneumonia and disseminated infection. They cause high morbidity and mortality despite the recent advances in antifungal therapy due to limited availability of safe and effective antifungal agents. *Aspirgillosis* may occur as locally invasive pulmonary and sinus disease and present extremely challenging management problems.[23] Surgical removal of the affected area may be necessary along with high dose Amphotericin B or Voriconazole and long term suppressive therapy.

Lymphoid Interstitial Pneumonitis (LIP)

LIP is the most common lymphoproliferative, noninfectious pulmonary problem seen in HIV infected children.[5] It has been found in up to 30-40 percent of HIV infected infants and children with pulmonary disease.[24] LIP describes a spectrum of disorders that involve pulmonary lymphocytic infiltrates with mature, predominantly CD8 T Lymphocytes, plasma cells and histiocytes in the interstitial lung parenchyma, alveolar septa and along the lymphatic vessels with hyperplasia of the pulmonary lymphoid tissue, termed Pulmonary Lymphoid Hyperplasia (PLH). It is classified as a Category B condition as per the CDC Classification and is attributed to and indicative of an HIV related immunological deficit. It also occurs in adults and HIV uninfected children, although uncommon. The exact etiology remains unknown, but appears to involve a multifactorial process involving HIV gene products and host responses and other pathogens. The pathogenesis of LIP may represent an atypical response to an inhaled or circulating antigen by a dysregulated immune system as a consequence of HIV infection. As per literature, Epstein-Barr virus is said to be often found in the lungs of children with LIP and AIDS, suggesting a possible role in pathogenesis.

The clinical manifestations can range from asymptomatic disease with isolated radiographic abnormalities to severe bullous lung disease with pulmonary insufficiency. The onset of LIP is often insidious and slowly progressive, usually in the 2nd or 3rd year of life and may be associated with mild cough, fatigue, dyspnea, tachypnea, symmetrical/generalized/painless/non matted lymphadenopathy, bilateral chronic non-tender parotid enlargement, hepatosplenomegaly and clubbing of fingers. The clinical course is highly variable in children, but generally benign and is said to be associated with prolonged survival.[24] It can resolve spontaneously, worsen episodically or slowly and progressively with intercurrent pulmonary infections and bronchiectasis. Auscultation of the chest is usually normal or may reveal crackles and wheezes. Oxygen desaturation with cyanosis may be present in more advanced stages of the disease. Serum IgG levels greater than 2500 mg/dL are strongly associated with LIP. Diagnosis is clinical as it can only be confirmed by lung biopsy. Typical Chest radiographic findings are bilateral diffuse reticulonodular infiltrates that are more prominent in the lower lobes and enlarged mediastinal / hilar lymph nodes, but may have no abnormalities other than hyperinflation. The radiographic

picture is often difficult to differentiate from other infectious pneumonias – miliary TB, Candida, CMV, etc. Bacterial pneumonia is a common complication although concurrent PCP is unusual. Chest Computed Tomography (CT) confirms the interstitial pattern and is useful for monitoring the severity and extent of the disease. A presumptive diagnosis of LIP can usually be made clinically and by persistent chest X-ray finding lasting more than 2 months, not responding to antibiotics and without other documented etiologies. Lung biopsy is the only definite way to establish the diagnosis, although it is rarely used.

Treatment of LIP is nonspecific. Although there have been no controlled studies to assess their efficacy, systemic corticosteroids are currently used for severely symptomatic LIP with significant hypoxemia and pulmonary insuffiency. Prednisolone 1-2 mg/kg daily may be given for 2-4 weeks and then tapered gradually over 2 weeks. Most children respond promptly to the treatment within the first few weeks, although some may be refractory to therapy. In refractory cases, the lowest possible dose that results in control of clinical symptoms may be continued for a period of 4-6 months. Oxygen, bronchodilators and other supportive measures may be required for severe hypoxemia episodes. LIP may be difficult to differentiate from PTB or miliary TB. Radiographic abnormalities are often unilateral with PTB. The important features that help to differentiate miliary TB from LIP are listed in Table 2.6.5.

Immune Reconstitution Inflammatory Syndrome (IRIS)

It is defined as a collection of signs and symptoms resulting from the ability to mount an immune response to antigens or organisms associated with immune recovery on ART.[25] It results in a paradoxical clinical deterioration after starting ART from an improving immune system (as evidenced by increase in CD4 counts from baseline prior to starting ART) interaction with organisms that have colonized the body during the early stages of HIV infection. Frequency is roughly 10 percent of all patients initiating ART and up to 25 percent among patients initiating ART with a CD4 cell count <50 cells/mm^3 or severe clinical disease.[26,27] IRIS may present weeks to months after starting ART, but usually presents within 6 weeks of starting ART. Care must be taken to differentiate IRIS from an opportunistic infection or drug toxicity and is a diagnosis of exclusion. IRIS is usually due to an active or sub clinical infection by an opportunistic organism, but may be due to noninfectious causes like sarcoidosis and auto- immune disorders. A wide range of pathogens cause IRIS like *Mycobacterium tuberculosis, Cryptococcus neoformans, Pneumocystis jerovecii, Mycobacterium avium* complex, *Candida albicans*, Aspergillosis, Hepatitis B/C, CMV, Herpes simplex, Varicella zoster, etc. Clinical presentations vary and depend on the causative agent and the organ system involved. For example, IRIS caused by *Mycobacterium tuberculosis* may present with high fever, lymphadenopathy, worsening of the original TB lesion and/or deteriorating radiographic manifestations, including the development of miliary pattern or pleural effusion. As IRIS is a newly recognized condition, there are no randomized clinical trials or formal recommendations to guide management. Management includes specific antimicrobial therapy for the offending organism with continuation of the ART under close monitoring. In severe cases glucocorticoids for 2-4 weeks with gradual tapering is usually effective and in severe cases temporarily discontinuing ART may help.

Table 2.6.5: Differentiation of miliary TB from LIP in children

Clinical features	*Miliary TB*	*LIP*
Respiratory symptoms	-/+	+++
Persistent fever	++	++
Wasting	+++	-/+
Generalized lymphadenopathy	-/+	+++
Parotid enlargement	-	++
Clubbing	-	+
Hepatomegaly	++	++
Acutely ill with CNS involvement	++	-
CXR features		
Diffuse micronodular (<2 mm)	++	+
Large uneven nodules	-	++
Diffuse reticular	-	++
Lymphadenopathy	-/+	++

Source: World Health Organization TB/HIV. A clinical Manual WHO/HTM/TB/2004.329 Geneva, Switzerland: WHO 2004

Bronchiectasis

Bronchiectasis is a permanent abnormal dilatation of the bronchi and usually results from a previous infectious process that damages the pulmonary mucosa and the bronchial wall, irreversibly altering its shape and function. This altered pulmonary architecture predisposes to recurrent infections. In HIV infected children it is usually a complication of LIP or TB. A cough productive of copious purulent and sometimes blood-stained sputum, finger clubbing, and halitosis are typical features. Although chest radiographs often reveal evidence of bronchial wall thickening (Fig. 2.6.8), the hallmark bronchodilatation may require confirmation by high resolution CT Scan. Management includes prompt anti- microbial therapy, aggressive chest physiotherapy and anti- inflammatory therapy if indicated in LIP or Asthma.

Chronic Respiratory Diseases

Many abnormalities of large and small airways as well as pulmonary parenchyma can produce chronic cough. Common etiologies without specific pulmonary disease include asthma, allergic rhinitis, chronic sinusitis, chronic bronchitis, foreign body aspiration and gastroesophageal reflux. Chronic sinusitis and chronic otitis media are a source of significant morbidity in HIV infected children. The development of chronic lung disease is common in HIV infected children. The spectrum of chronic HIV associated lung disease includes LIP, chronic infections, IRIS, bronchiectasis, malignancies, and interstitial pneumonitis. Underlying cardiac disease should always be considered in the differential diagnosis of respiratory problems in HIV infected children. Cardiomyopathy may occur as a primary manifestation of HIV disease or drug exposure (extensive exposure to Zidovudine). Children may present with recurrent episodes of tachypnea, dyspnea, bibasal rales, wheezing, etc with a radiographic picture of bilateral increased interstitial markings with or without cardiomegaly. The diagnosis is confirmed by Echocardiography. Children with HIV who survive longer are less likely to die of pulmonary disease or infection and more likely to die of cardiac causes or with wasting syndrome.[3] Chronic lung disease may result from recurrent or persistent pneumonia due to bacterial, mycobacterial, viral, fungal or mixed infections. In high TB prevalence areas, *M. tuberculosis* is an important cause of chronic respiratory illness. Diagnosis of chronic lung disease is based on chronic symptoms and persistent chest X-ray changes but definitive diagnosis can be difficult as clinical and radiological findings may be non-specific. Treatment includes therapy for specific infections, pulmonary clearance techniques, corticosteroids for children with IRIS or LIP who are hypoxic or who have airway compression from tuberculous nodes and ART. Preventative strategies include immunization, chemoprophylaxis, and micronutrient supplementation. Early use of ART may prevent the development of chronic lung disease.[28]



Fig. 2.6.8: The cystic (honeycombing) changes characteristic of bronchiectasis can be seen in the right middle and lower lobes. The arrow indicates the cystic changes

Pulmonary Malignancies

Although there is an increased incidence of malignancies in HIV infected population, it is generally rare in the pediatric population. Pulmonary malignancies may present as hilar adenopathy, mediastinal masses, isolated parenchymal nodules, or diffuse interstitial disease incidentally found on chest radiographs. It may include Non Hodgkin's Lymphoma, tumors of smooth muscle origin, Mucosa Associated Lymphoid Tissue lesions, or pulmonary Kaposi's Sarcoma. It can involve the lungs and causes diffuse lung infiltration and lymph node enlargement. Patients may present with a large pleural effusion which is bloody on aspiration. Presence of typical lesions on the skin, palate or conjunctiva may give clue to the diagnosis. Lung biopsy is always required for definitive diagnosis.

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2.7

Cardiac Manifestations in HIV Infected Children

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Introduction

Since the introduction of antiretrovirals, the mortality from HIV and incidence of new infections has decreased substantially. However, globally there are 33 million people living with HIV[1] and 50 percent of those are women. A large portion of these patients (22 million) are living in sub-Saharan Africa. The number of children living with HIV is 2 million, of which 90 percent are living in sub-Saharan Africa. It is estimated that 370,000 children under the age of 15 are infected with HIV every year.

The introduction of highly active retroviral therapy regimens (HAART) has significantly changed the course of the disease and lengthened the survival and quality of life of HIV infected patients. Use of antiretroviral medications in low and middle income countries has increased ten-fold in 6 years, reaching almost 3 million people by the end of 2007. Unfortunately, HAART therapy is still not available to a large number of patients. Studies performed in the United States in the pre HAART era, are therefore still applicable to this population.

Cardiac Involvement

HIV is a multisystem disease with frequent cardiac involvement. With introduction of antiretrovirals and improved survival, there are concerns about long-term issues that may arise from effects of HAART on the heart and long-term cardiovascular outcomes. With improved survival, cardiovascular morbidity is becoming a significant concern. Cardiac dysfunction occurs in 18-39 percent of HIV infected children and is associated with increased risk of death, in almost one-third of patients.[2] Congestive Heart Failure (CHF) is noted in 5-14 percent of patients.[3]

Cardiac Manifestations

Cardiac disease is the underlying cause and important contributing factor to mortality. Children with HIV have significantly high incidence of cardiac dysfunction and as per the P2C2[4] (Pulmonary and Cardiac Involvement in HIV) study, where increased heart rates, decreased shortening fraction and increased left ventricular mass and wall thickness was reported.[4] Cardiac manifestations can be dilated cardiomyopathy, myocarditis, endocarditis, pericardial effusions, pulmonary hypertension, drug-related cardiotoxicity and arteriopathy and coronary artery disease.[5-8] Infants born to HIV infected mothers are at increased risk of cardiac abnormalities regardless of their HIV status.[9]

Dilated Cardiomyopathy and Myocarditis

Dilated cardiomyopathy is the most common cardiac abnormality in patients with HIV infection, resulting in increasing the mortality to four-fold. In a population with similar stage of HIV infection, there was a median survival of 101 days in patients with HIV associated left ventricular dysfunction, and a median survival of 472 days in patients without cardiac involvement.[10] In the prospective P2C2 HIV study, mortality was higher in patients with baseline depressed left ventricular shortening fraction or increased left ventricular dimension, thickness, mass and wall stress.[4] In 205 children with documented vertically transmitted HIV infection who were followed for ~10 years, it was noted that even mild left ventricular dysfunction and mildly increased left ventricular mass were risk factors for early mortality.[11]

Cardiac performance is determined by preload, afterload, contractility and heart rate. In the presence of disturbance in myocardial contractility, the heart depends on a number of adaptive mechanisms such as, increasing preload (salt and water retention), myocardial hypertrophy and increased release of catecholamines. However, the capacity of these mechanisms is finite and congestive heart failure can ensue. Patients with HIV can develop rapid or chronic onset congestive heart failure. Patients with rapid onset heart failure can die within 6-

12 months after diagnosis of CHF. Chronic onset has better prognosis and responds better to medical therapy.[12,13]

Myocarditis is a cause of the dilated cardiomyopathy seen in HIV. HIV virus itself can cause myocarditis either directly or indirectly via autoimmune process, or there could be infection with other viruses such as CMV, coxsackie virus, herpes virus and bacteria as *Mycobacterium tuberculosis* and *avium* and some protozoa and fungi. Cardiac-specific autoantibodies were reported in HIV patients especially in patients with cardiac dysfunction supporting the theory that autoimmunity has a role in the development of cardiac disease. Cytokines can play a role in HIV associated myocarditis. Viral infection in the context of a nonspecific stimulator of monokines as IL-1 or TNFα is more likely to lead to myocarditis and myocyte damage than viral infection alone. Patients with HIV cardiomyopathy who also had infection with CMV or coxsackie virus, had samples that stained more intensely for TNFα and inducible nitric oxide synthase (iNOS).[6]

There are studies reporting that patients with encephalopathy are more likely to die of congestive heart failure, than patients without encephalopathy. In the prospective P2C2 HIV multicenter study, HIV children who developed encephalopathy had lower shortening fractions that declined rapidly, and in the Mothers and Infant transmission study, dilated cardiomyopathy was present in 30 percent of children with Encephalopathy compared to 2 percent without encephalopathy. There are speculative mechanisms to support the cause and effect, but more investigations are warranted.

Pathophysiology

Cardiac involvement is related to either direct action of HIV on the myocardium or to an autoimmune process induced by HIV. There is a possible causative etiology contributed by cardiotropic viruses as in coxsackie virus B3 and cytomegalovirus. Other pathogenic factors include apoptosis and other adverse effects induced by viral proteins and virus induced transcriptional activation of various cellular genes.[14] As the HIV disease progresses, immunodeficiency may enhance the pathogenic activity of both HIV and cardiotropic viruses and influence their clinical evolution. Both cellular and humoral immunity are implicated in progression and cardiac involvement. Inflammatory cell infiltrate CD3 and CD8 lymphocytes have been implicated as have major histocompatibility complexes (MHC)-I in 70 percent of both HIV associated and idiopathic dilated cardiomyopathy.

Micronutrient deficiency of selenium, carnitine and thiamine can also result in decreased cardiac function. Nutritional deficiencies are observed in patients with HIV and low levels of selenium were noted in pediatric AIDS patients. In wasting patients, selenium replacement can restore ventricular function and reverse cardiomyopathy. In developing countries, selenium deficiency plays an important role in HIV related cardiomyopathy as was reported from a study in Rwanda.[15] Other nutritional issues contributing to cardiac dysfunction are vitamin B, folate and zinc deficiencies.

Use of zidvidine and its association with dilated cardiomyopathy had been reported based on the hypothesis that it influences destruction of cardiac mitochondrial infrastructure and inhibition of mitochondrial DNA.[16]

Pericardial Disease

Pericardial disease is often encountered in HIV patients. The prevalence is estimated to be 22 percent in asymptomatic HIV infected adults and somewhat less in children.[16,17] This usually ranges from asymptomatic pericardial effusions to significant large effusions that compromise cardiac output. Constrictive pericarditis is rare but tuberculosis and other opportunistic infection, and cancer may present with effusive, constrictive pericardial disease in this immunocompromised host

Coronary Artery Disease

As patients with HIV are living longer, chronic cardiac complications arise such as coronary artery disease. It has become clear that patients with HIV are at increased risk for cardiovascular events. Even though reports are conflicting, the majority of studies suggest that HAART regimen increases cardiovascular risk and risk for Myocardial Infarction.[8] In an autopsy study of young to middle aged patients who died of advanced AIDS, HIV patients had 3 times the odds of having significant stenosis of the coronary arteries. In children, arteriopathy is increasingly recognized and there are two different types of arteriopathy, one involving the coronaries and the other involving large vessels as the aorta and pulmonary arteries.[18]

HAART can increase cardiovascular risk by influencing the lipid profile of the patient. In the early phase of the disease there is hypertriglyceridemia, low HDL, and low LDL.[19] After treatment with HAART, LDL and total cholesterol can increase with no change in HDL cholesterol. There can be hypertriglyceridemia, and specifically the protease inhibitor (PI) Ritonavir has been associated with increases in triglycerides and in some cases with extreme hypertriglyceridemia exceeding 1,500 mg/dl.[15]

Certain combinations of HAART are strongly associated with lipodystrophy, a condition with uniform subcutaneous fat loss with relative preservation or increase

in visceral fat, resulting in central adiposity and accumulation of fat in the neck area and dorsocervical region. It is associated with metabolic syndrome which consists of insulin resistance, impaired fasting glucose tolerance test, elevated triglycerides, low HDL and hypertension. HIV patients have high prevalence of metabolic syndrome. In a study of 710 patients, 17 percent had metabolic syndrome.[8] Progression to metabolic syndrome is very substantial in the first 3 years after HAART treatment. Non-nucleoside reverse transcriptase inhibitor therapy (NNRTI) may have a beneficial effect by increasing the HDL cholesterol.[19] With early recognition of lipid derangements and metabolic syndrome, modification of anti-retroviral therapy (ART) should be considered.

Cardiac Involvement with Vertical Transmission

HAART has significantly decreased the rate of vertical transmission of HIV. But children exposed to this treatment *in utero* are at increased risk of toxicity and cardiac complications. Infants born to HIV infected mothers are at increased risk of cardiac abnormalities regardless of their HIV status.[9] Animal and human studies suggest that HAART can cause mitochondrial dysfunction. Mitochondrial dysfunction in cardiomyocytes could result in cardiomyopathy and congestive heart failure. However, in a prospective study of 382 infants born to HIV infected mothers, *in utero* exposure to zidovudine was not associated with acute or chronic abnormalities in cardiac structure or function.[20] Intrauterine exposure to antiretrovirals and cardiovascular involvement needs to be further investigated. In recent data from the CHAART-I (Cardiac status of HAART exposed infants—born to HIV infected mothers) showed that the incidence of cardiac dysfunction and decreased ventricular mass was seen in HIV negative infants born to mothers with prenatal exposure to HAART therapy compared to those HIV negative infants who did not have *in utero* exposure to HAART therapy.

Pulmonary Hypertension

Pulmonary hypertension is observed in increased numbers in HIV patients. The incidence is 1/200,000 in the general population and 1/200 in HIV patients.[21] It is occurring at a younger age than the general public and has been reported in patients with lung infections, venous thromboembolism and left ventricular dysfunction. Symptoms can range from asymptomatic patients to severe cor pulmonale.

Cardiac Tumors

AIDS associated tumors as Kaposi sarcoma can affect the heart (as a disseminated process) and are usually localized in the epicardial space and typically do not involve the myocardium or parietal epicardium. Also, primary or metastatic lymphomas of the heart have been reported. These can involve the pericardium and myocardium.

Autonomic Dysfunction

HIV infection can be associated with autonomic dysfunction and patients have been noted to have increased incidence of syncope, postural hypotension, diminished sweating, and rhythm abnormalities.[22] Sinus tachycardia and prolonged QTc are also observed.[23] QT interval prolongation is possibly related to medications or to an acquired form of prolonged QT syndrome. As reported in a study in children, there is autonomic involvement in HIV, independent of cardiac dysfunction.[22] The clinical implication of this is unclear as none of those patients were symptomatic.

Endocarditis

Endocarditis has been noted in HIV patients, with the same incidence as in patients with risky behaviors (drug abusers). Infectious agents most commonly involved are *Staph. aureus*, *Strep. pneumoniae*, *Haemophilus influenzae* and the HACEK group, *Cryptococcus* and *Candida*. *Candida* of the oral cavity and esophagus is the primary focus and can become a systemic illness. The right sided valves are usually involved and vegetations of the tricuspid and pulmonary valves can embolize to the lungs. Systemic emboli can involve the coronary arteries, spleen, bowel, extremities and central nervous system. Patients with HIV have same presentation and survival as patients without HIV and endocarditis. But in late-stage disease, mortality is 30 percent higher than in asymptomatic HIV patients.[21]

Arteriopathy

There has been documentation of aortic root dilation in children with vertically transmitted HIV infection. The aortic root dilation was associated with left ventricular dilation and increased viral load and lower CD4 count in HIV infected children.[18]

Symptoms

Patients could develop shortness of breath, exercise intolerance and palpitations. Unfortunately, these symptoms could be caused by other HIV related

complications. Recommendations in evaluating the patients include thorough history and physical exam, to identify cardiac and non-cardiac disorders and assessment of patient's ability to perform daily activities.[24]

Assessment

History and physical exam might not be sufficient in HIV patients, to assess the cardiovascular status. Often symptoms and physical findings can be caused from pulmonary or cardiac etiology. Evidence supports that a number of different screening tools should be used.

Echocardiographic monitoring is recommended as baseline and every 1-2 years in asymptomatic individuals and yearly in individuals with symptomatic HIV infection. When the echocardiograms are abnormal, follow-up should depend on cardiologist's recommendation.[24] Echocardiography can detect valvular heart disease, vegetations associated with endocarditis, left ventricular hypertrophy and dilatation and systolic and diastolic dysfunction. Information on pulmonary hypertension and pericardial effusions can also be obtained.

Electrocardiograms can be helpful for rhythm issues associated with this disease. Routine use of electrocardiography and holter monitoring may not be indicated.[25] Left ventricular dilatation is the most common finding and ECG was demonstrated to be a poor indicator of echocardiographic LVH, in patients with vertically transmitted HIV.[26] Holter is indicated for patient with symptoms of palpitations, syncope or presyncope or autonomic dysfunction and patients on medications that can affect the QT interval.

Stress testing may be helpful to assess left ventricular dysfunction and to screen for premature atherosclerosis.

Cardiac catheterization is indicated when there is a need for further diagnostic testing as endomyocardial biopsy for patients with deteriorating conditions for whom differential diagnosis could be made between CMV myocarditis versus mitochondrial toxicity from antiretrovirals. Angiography is indicated in patients with suspected coronary disease, where revascularization would be beneficial.

And lastly, pericardiocentesis could be helpful in diagnosis of treatable opportunistic infections and malignancy.

Blood Chemistry

Before therapy with HAART is initiated, fasting baseline lipid profiles and serum glucose and hemoglobin A1c should be checked. Measurements should be repeated routinely while patients are on the medications. For protease inhibitors (PIs), the follow-up should be every 3-6 months after initiation of treatment.

Treatment

For patients with asymptomatic left ventricular dysfunction, it is recommended, but not mandated to treat with ACE inhibitors and or beta blockers. For symptomatic left ventricular systolic dysfunction it is recommended to treat with diuretics, ACE inhibitors, β-blockers and digitalis. For patients with lipid abnormalities when exercise and diet are not enough, drug therapy with statins and/or fibrates might be indicated if antiretroviral therapy cannot be changed.[1] Carnitine, selenium and multivitamin supplements should also be considered.

Summary

In the current era, the spectrum of cardiac involvement and disease severity in children with HIV is undergoing a process of continual evolution. With the advent of HAART medications, the survival of HIV patients has improved significantly and the prevalence of chronic conditions such as subclinical cardiac dysfunction, coronary artery disease will increase. Lipodystrophy, metabolic syndrome and abnormal fat distribution are now seen in patients on PIs and nucleotide reverse transcriptase inhibitor therapy (NRTI). Historically, patients with HIV infection and cardiac involvement have poorer prognosis. Hopefully, HAART medications will improve the course of the disease and reduce the incidence of effusions, cardiac malignancies and co-infections. There is ongoing effort and multicenter studies such as, SMART (Surveillance Monitoring for ART Toxicities) and AMP (Adolescent Master Protocol Study) that are evaluating children and adolescents between the ages of 7-16 years who had had prenatal exposure to antiretroviral therapy with close cardiovascular surveillance.

Close cardiac monitoring of HIV patients is indicated and this should involve yearly echocardiograms, EKG and blood work for lipid derangements. Use of serum biomarkers such as BNP and pro-BNP for evaluation and monitoring of congestive heart failure in this population subset has not been adequately evaluated. Holter monitoring, exercise stress testing, and angiography are to be reserved for a subset that has symptoms suggestive of autonomic derangements, arrhythmia, and coronary artery disease.

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2.8

Hematological Aspects and Management of Pediatric HIV Disease

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Introduction

HIV infection and treatment for HIV cause a wide range of hematological abnormalities.[1,2] The predominant mode of transmission in children is perinatal exposure to an infected mother but another important route is through the use of infected blood and blood products. Early sexual activity and sexual abuse are other routes. The infection rates of mother to child transmission have decreased from about 25 percent to about 2 percent in well resourced countries.[3,4] Higher rates of infection occur when prevention programs are weak. Early infection (fetus and infant) is associated with rapid disease progression.[5]

Patients requiring frequent blood transfusions (e.g thalassemia major or hereditary aplastic anemia) or frequent use of blood products (e.g. haemophilia) are at increased risk. Use of fresh blood and pooled product increase the risk. The chances of infection with the transfusion of an infected unit is about 90 percent; however the risk of transmission is approximately one in 493,000 units where the HIV incidence is low.[6] The South African experience has shown that in 1998 when 0.26 percent of blood donations were HIV positive the residual risk of HIV infection was estimated at 3.4 per 100,000 donations. Despite individual donor nucleic acid testing with reduction of the window period to approximately 5.6 days the residual risk of HIV infected units is one in 100,000 donations.[7] Additional strategies implemented to improve blood safety include donor screening, questionnaires, deferred donations, limiting donor exposure and quarantine of product until a subsequent donation.

The experience at our center in Durban, South Africa is likely to be mirrored by other centers in the developing world. In a review of 160 patients referred to our unit for investigation of hematological problems (mainly cytopenias) the pattern was as follows:

• Pancytopenia	18
• Anemia	43
• Thrombocytopenia	10
• Anemia + thrombocytopenia	61
• Neutropenia alone	0
• Neutropenia + thrombocytopenia	1
• Neutropenia + anemia	7

Following exposure there is primary infection (an acute retroviral syndrome) followed by a variable period of clinical latency and then symptomatic infection. The primary infection includes fever, rash, upper respiratory symptoms and cervical adenopathy.[8] Atypical lymphocytes and transient cytopenias may occur. Cytopenias increase as HIV infection progresses to AIDS. Recognising that many patients in the developing world are being offered antiretroviral therapy (ART) it is important to identify and treat coexisting conditions which are present prior to initiation of ART and to be aware of the impact therapy has on the bone marrow and blood. Delay in the initiation of ART is sometimes accompanied by significant morbidity and delay in recovery of certain lineages like CD4-lymphocytes and platelets.

The aspects to be covered include the following:
- The immune system
- The bone marrow in HIV infection
- Pathogenesis of cytopenias
- Anemia
- Thrombocytopenia
- Neutropenia
- Coagulation abnormalities.

Immune System

Advancing HIV disease is characterized by progressive depletion in the CD4-lymphocytes due to HIV infection. Factors that contribute to the CD4-lymphopenia include the direct cytopathic effect of infection in these cells, HIV specific antibody-mediated and cytotoxic T cell mediated mechanisms, impaired production of stimulatory cytokines and inhibition of T-lymphocyte proliferation.[9,10] An increase in the CD8-lymphocytes occurs initially and the CD4:CD8 lymphocyte ratio reverses.

B-lymphocyte dysregulation results in polyclonal B-lymphocyte activation with accompanying hypergammaglobulinemia, increase in autoimmune phenomena and risk of B-cell lymphoma.[11,12]

Natural killer cell activity is decreased with HIV infection.[13] HIV infects reticuloendothelial cells expressing CD4 (monocytes, macrophages and follicular dendritic cells). The dendritic cells are important in HIV clearance while monocytes and macrophages may serve as a reservoir for the virus.[14]

Bone Marrow in HIV Infection

Constitutive production of constituents of the blood is under the control of Colony Stimulating Factors (CSFs). CSF includes granulocyte, macrophage, granulocyte-macrophage stimulating factor, stem-cell factor, thrombopoietin and erythropoietin. CSFs regulate both the production with passage of hemopoietic cells into the cell cycle and the terminal maturation of marrow elements. Inducible production is largely controlled by cytokines and interleukins. Growth factors and cytokines are produced by the cellular component of stroma. In addition endogenous cytokines are released from the marrow in response to many stimuli.

HIV infection of the accessory (stromal) cells in the bone marrow is probably more important than infection of the progenitor cells. HIV does not infect the mature red blood cells and neutrophils. HIV infection usually targets the monocytes because of the presence of CD4 antigen. Monocytes are relatively resistant to the cytopathic effects of HIV. Monocytes are central in the control of hemopoiesis by production of cytokines, interleukins and growth factors. HIV infected mononuclear cells inhibit hemopoiesis by cell-to-cell interactions as well as by producing inhibitory cytokines. IL-1 and TNF are high with HIV infection and both induce interleukin-2 (IL-2) with increased production of interferon-alpha (IF-α). HIV infected monocytes also produce transforming growth factor β (TGF-β).

IF-α and TGF-β are potent suppressors of hemopoiesis. These inhibit the production of growth factors from other cells, and may directly inhibit the progenitor cells themselves. HIV can directly infect early myeloid progenitor cells and megakaryocytes. The binding site for HIV (gp120) is the surface CD4 receptor. For entry coexpression of specific chemokine receptors (CXCR4, CCR5) is needed. This determines the trophism of the virus - X4 (T- trophic); R5 (M-trophic); and R5X4 strains. Hemopoietic progenitor cells (CD34+ cells) co-express CD4, CXCR4 and some CCR5. Infections (CMV, HHV6, TB) upregulate HIV receptors and render progenitor cells permissive to direct HIV infection.

Trilineage dysplasia in the bone marrow is the hallmark of advancing HIV infection and the severity increases with disease progression.[15] These changes are found in almost all patients with HIV infection even in the absence of other pathological processes and routine bone marrow examination is not recommended.[16] The sampling is most informative when looking for a specific etiology for cytopenia (TB, CMV, parvovirus) or to exclude bone marrow infiltration; special stains and cultures for fungi, viruses and mycobacteria are useful. *Cryptococcus neoformans* and *Histoplasma capsulatum* may be found in macrophages, and viral inclusions may be seen in CMV and Parvovirus infection. A definitive diagnosis of CMV, Parvovirus and herpes simplex by PCR may be made on the bone marrow aspirate. Trephine biopsy is useful for assessment of granulomas, detection of acid fast bacilli (AFB) and for marrow infiltration.

Non-specific changes that occur are mild hypercellularity and hypocellularity in some patients, normocellularity in the majority, and an increase in lymphocytes mixed with plasma cells, eosinophils, macrophages, epithelioid cells and fibroblasts. Reticulin is often increased and there may be collagen fibrosis. Aplasia is uncommon but in certain settings pure red cell aplasia occurs. Bone marrow atrophy or degeneration may be present in late AIDS.

With parvovirus B19 infection there is PRCA and giant pronormoblasts with basophilic clumped chromatin and clear cytoplasmic vacuoles with viral inclusions are present.[17] With autoimmune hemolytic anemia (AIHA) erythroid hyperplasia is usually present and associated infection like CMV and tuberculosis have to be excluded.

Bone marrow examination is indicated in:
- 2 or more cytopenias
- Investigation of opportunistic infection and PUO
- Exclusion/staging of malignancy
- Diagnosis of specific pathology like red cell aplasia or megaloblastic anemia.

Pathogenesis of Cytopenias

Various factors are implicated in the development of cytopenias (Table 2.8.1).

Table 2.8.1: Pathogenesis of HIV associated cytopenia

- Direct effect of HIV infection of progenitor cells
- Indirect effects on BM-cytokines like TNF; reticulin fibrosis
- Altered immune function-antibody production
- Micro-nutrient deficiency (folate, vitamin B_{12}, and iron)
- Coinfection (TB, CMV, EBV, Parvovirus)
- Infiltration by malignancy (non-Hodgkin lymphoma, rarely Kaposi sarcoma)
- Drugs (Co-trimoxazole, zidovudine)
- Anemia of chronic disease
- Complex, often with many factors

Anemia

Anemia occurs at all stages of HIV infection and is present in 63 to 95 percent of infected persons at some point; the incidence increases with disease progression and 37 percent of those with clinical AIDS have anemia.[18] The presence of anemia and persistent anemia are associated with an increased risk of death.[19,20]

The main etiologies are hematinic deficiency, infections and drugs (Table 2.8.2). Bone marrow stem cells are relatively resistant to HIV infection and factors contributing to the anemia of chronic disease are cytokines associated with HIV infection and a blunted response and production of erythropoietin.[21] The major cytokines are transforming growth factor-beta (TGF-β), tumor necrosis factor (TNF) and interleukin-1 (IL-1).

Zidovudine (AZT) is the main drug implicated in anemia and causes a macrocytic anemia in a dose dependent manner.[22] Higher doses cause anemia needing transfusion. Other drugs causing anemia include ganciclovir, amphotericin B and trimethoprim.

Opportunistic infections contribute to cytopenias. Sometimes multiple infections are present. In developing countries *Mycobacterium tuberculosis* (TB) is a common infection. Atypical mycobacteria, especially mycobacterium avium complex (MAC), occur when there is severe immunosuppression. Bone marrow biopsy is more useful to document marrow involvement by mycobacteria; appearances may be atypical with ill-formed granulomas. Culture is obligatory.[15]

Cytomegalovirus (CMV) and EBV infections are common childhood viral infections which suppress the bone marrow. Polyclonal activation of B-lymphocytes with an autoimmune hemolytic anemia and large splenomegaly are contributory causes.

Table 2.8.2: Anemia and HIV infection

Decreased production
• Drugs-Zidovudine, Cotrimoxazole, Amphotericin B, Gancyclovir, Dapsone
• Deficiencies-Erythropoietin, Iron, Folate, Vitamin B_{12}
• Infection-HIV, CMV, EBV, Parvovirus B19, Mycobacterium tuberculosis, Mycobacterium avium complex, Histoplasma capsulatum
• Neoplasia-Hodgkin's disease, Non-Hodgkin's lymphoma
• Miscellaneous - Anemia of chronic disease,
Increased loss/destruction
• Hemolysis-Autoimmune hemolytic anemia, TTP, DIC, infections, pre-existing conditions (glucose-6-phosphate dehydrogenase deficiency, sickle cell disease, thalassaemia, etc.)
• Gastrointestinal bleeding–Infections (CMV, Candida, parasites), Kaposi sarcoma, bowel lymphoma
• Hypersplenism–Infection, Haemophagocytosis, Lymphoma
• Idiopathic

Pure red cell aplasia (PRCA) is not uncommon. Apart from drugs (AZT, trimethoprim) human parvovirus B19 is the major infectious cause. Parvovirus B19 infection targets the pronormoblast and causes lytic infection.[17] HIV infected infants with immune suppression or with no prior exposure to parvovirus appear to be at increased risk of PRCA.[23] Diagnosis is confirmed by bone marrow biopsy and PCR or FISH. Intravenous immunoglobulin containing antibodies from donors exposed to parvovirus is indicated and repeated infusions may be needed.

Autoimmune hemolytic anemia may be the result of autoantibodies to red cell antigens. A positive Coombs' test is presented in up to 77 percent of patients.[24] Severe hemolysis occurs in some patients while in others positive Coombs' test accompanies the polyclonal hypergammaglobulinemia but there is no significant hemolysis. Cold agglutinins, commonly anti-I and sometimes anti-I or anti-Pr, and sometimes hemolysis may occur with some infections like mycoplasma. Clues to the presence of hemolysis are a high reticulocyte count, elevated LDH and falling hemoglobin. The smear usually shows spherocytes. Caution is needed in interpreting a low reticulocyte count when parvovirus infection or hematinic deficiency is present. In rare cases red cell aplasia responsive to steroids may occur with AIHA.[25] Other causes of increased red cell destruction include TTP, DIC, and pre-existing causes like G6PD deficiency and hemoglobinopathy.

Hematinic deficiency (folate and Vitamin B_{12}) causes ineffective hemopoeisis affecting all cell lines. Factors contributing to folate deficiency include poor diet, poor apetite and intestinal disease including chronic diarrhea. Vitamin B_{12} malabsorption may occur with gastric pathology (achlorhydria), antibodies (parietal cell, intrinsic factor), bacterial overgrowth and disease of the terminal ileum. Vitamin B_{12} deficiency may be subclinical but must be excluded in the presence of cytopenias and neurologic dysfunction. Iron deficiency occurs with chronic blood loss and intestinal parasites and supplementation with iron is recommended when iron deficiency is confirmed or with chronic blood loss.

Production of erythropoeitin (EPO) is suboptimal in HIV infection due to infections and cytokine effects.[20] Exogenous EPO at a dose of 100-200 U/kg three times weekly is of benefit in persons with low endogenous EPO levels (<500 U/l) and in drug induced marrow suppression (zidovudine, chemotherapy).

Approach to a patient with anemia

An approach to anemia begins with an assessment of red cell production. Using the corrected reticulocyte count or the degree of polychromasia three groups are identified:

- Patients with increased red cell production – reticulocyte count >2 percent or with marked polychromasia

- Patients with reduced red cell production – reticulocyte count <1 percent or absent polychromasia
- Patients with normal but inadequate red cell production – reticulocyte count 1 to 2 percent.

Increased red cell production occurs in response to hematinic therapy, hemorrhage or with hemolysis. Chronic blood loss results in iron deficiency while acute or recent blood loss results in a normocytic normochromic anemia. Investigation of a hemolytic process includes examination of the blood smear and a Coombs' test. The presence of red cell fragmentation with low platelets suggests a microangiopathy and HUS and TTP need to be excluded. Clues to an underlying hemolytic anemia (spherocytosis, sickle cell disease or G6PD deficiency) may be present. When the Coombs' is positive an autoimmune hemolytic anemia (AIHA) is likely. Autoantibodies may be part of a non-specific hypergammaglobulinemia and in many cases are not clinically significant. The antibodies may be warm or cold antibodies and there may also be cold agglutinins. The presence of significant hemolysis may be inferred by a high reticulocyte count, elevated bilirubin, elevated LDH and/or the presence of spherocytes. A low reticulocyte count may mislead when there is hematinic deficiency, with parvovirus infection, with impaired erythropoietin (EPO) response and in some severe AIHA when red cell antibodies presumably target the progenitor cells.

With reduced red cell production (reticulocytes <1%) there is inadequate marrow response. Causes include hematinic deficiency, suppression of progenitor cells, impaired EPO production/EPO antibodies, bone marrow infection or infiltration or drug induced bone marrow suppression or pure red cell aplasia (PRCA). Common infections include CMV, tuberculosis, mycobacterium avium complex and parvovirus. Bone marrow examination is warranted in many of these patients.

Parvovirus has a predilection for young red cells (presence of the P antigen) and causes a lytic infection. With chronic infection red cell aplasia occurs. Serology including parvovirus IgM may not be reliable in the immunocompromised and PCR testing is recommended. The bone marrow may also show characteristic giant pronormoblasts and viral inclusions. Red cell aplasia is often only suspected when the patient needs repeated transfusions. The clinical presentation with drug induced red cell aplasia is identical and drug-induced disease is likely when studies for parvovirus are negative. Zidovudine (AZT), lamivudine (3TC), cotrimoxazole, ganciclovir and amphotericin B can cause red cell aplasia. Initial approach to the problem would be to identify and replace the offending agent. Lamivudine is one of the main drugs implicated in our experience and replacing this agent often requires a change in the regimen being used.

Treatments used in PRCA due to parvovirus include intravenous immunoglobulin and commencement of ART. With drug-induced PRCA stopping the drug is accompanied by a slow recovery of the anemia. Repeated red cell transfusions may be required and with nonresponse or slowly responding patients exogenous EPO is indicated.

With inadequate red cell production the mean corpuscular volume (MCV) guides the approach. A microcytic hypochromic anemia is commonly due to the anemia of chronic disease (ACD) or iron deficiency. The majority are ACD. Blood loss is an important factor for iron deficiency even in children and a search for the etiology includes gut parasites, infections like CMV, associated thrombocytopenia and malignancy. The anemia of chronic disease may be a microcytic hypochromic or normocytic normochromic anemia (NNA). Other features of ACD are mild to moderate anemia (Hb 8-12 g/dl), mild microcytosis (MCV rarely <74fl), normal iron studies (serum iron normal, ferritin normal or increased), raised markers of inflammation and nonresponse to iron. With NNA when the Hb is >10 g/dl and no other cell lines are affected the anemia is often ACD.

Causes of a macrocytic anemia include megaloblastic anemia, hemolysis, drugs and liver disease. Vitamin B_{12} and /or folate deficiency may be due to dietary deficiency or gastric, jejunal or ileal disease with malabsorption. Increased reticulocytes and a secondary folate deficiency contribute to macrocytosis when there is hemolysis. Drugs that cause macrocytosis include AZT, didanosine, lamivudine and ganciclovir.

Thrombocytopenia

Thrombocytopenia is relatively common (~40% of patients), increases with disease progression and is also associated with shortened survival.[26] In about 10 percent of patient it is the presenting manifestation.[27] During the latent period an immune thrombocytopenia may herald the development of AIDS.[2]

The commonest cause of primary HIV associated thrombocytopenia is immune-mediated destruction. This is commonly associated with high levels of platelet-associated IgG and immune complexes. Antibodies induced by HIV glycoprotein 120 which cross react with platelet glycoprotein (GP IIIa) and/or antibodies to GP IIb are implicated.[28] HIV infection of the megakaryocyte is a likely cause in some patients. Megakaryocyte expression of CD4 receptors, internalization of the virus and expression of CXCR4 on the progenitor cells have been demonstrated.[29-31] Reduced production and platelet lifespan are present.[27] Other secondary causes of reduced mean platelet survival and decreased production resulting in thrombocytopenia are listed in Table 2.8.3.

Table 2.8.3: Thrombocytopenia and HIV infection

Decreased production
• Drugs: Ganciclovir, Co-trimoxazole, Fluconazole, Aciclovir, Rifabutin, Clarithromycin, Didanosine, chemotherapy
• Deficiencies: Vitamin B_{12}, Folate
• Infection: HIV, CMV, MTB, MAC, Histoplasma capsulatum
• Neoplasms: Non-Hodgkin's lymphoma, Hodgkin's disease
Increased loss/destruction:
• Immune thrombocytopenic purpura
• Disseminated intravascular coagulation (DIC)
• Thrombotic thrombocytopenic purpura (TTP)
• Haemolytic uremic syndrome (HUS)
• Hypersplenism: infection, hemophagocytosis
• Drugs: Interferon, Saquinavir

When the platelet count is $<20\times10^9$/l and in patients who are bleeding treatment is indicated. Stop drugs that may be causing the problem. An immune thrombocytopenia is present in many patients and therapy with steroids or intravenous immunoglobulin (IVIg) is indicated. Steroids (prednisone 1 mg/kg/day) are useful but care needs to be exercised as underlying disease may worsen (CMV, TB, Kaposi) and patients are predisposed to fungal infections. Appropriate prophylaxis is indicated when commencing steroids. IVIg will be effective in many patients but is expensive and the effect in most patients is transient. IVIg is useful with acute bleeding and preoperatively and additional platelet transfusion may be required. The effect of platelet transfusion only is limited and its use is restricted to acute bleeding. In the older patients splenectomy is a consideration. Treatment for underlying opportunistic infections, HUS or TTP, and initiation of ART must be considered in all patients.

Neutropenia

Neutropenia often has a multifactorial etiology (Table 2.8.4). In common with the other cytopenias neutropenia increases with HIV disease progression.[32] There is decreased production of growth factors (GM-CSF and G-CSF) and in some patients their inhibition.[33,34] Haematinic deficiency (folate, vitamin B_{12}), opportunistic infections (*Mycobacterium tuberculosis*, *Mycobacterium avium* complex, CMV, EBV) and drug-induced neutropenia are other factors. The main drugs inducing neutropenia are zidovudine, gancyclovir, cotrimoxazole, acyclovir and cytotoxic chemotherapy. A functional defect affecting phagocytosis and killing of pathogens is also present.

Risks of bacterial infection increase with increasing severity of the neutropenia (moderate absolute neutrophils $<1.0\times10^9$/l and severe $<0.5\times10^9$/l).[35] During infections there may be a reversible fall of the neutrophil counts to very low levels. G-CSF administration has been demonstrated to increase neutrophil counts without enhanced replication of HIV and the dose required (1mcg/kg/day) may be much lower than conventional doses.[36] Care must be taken to avoid an increased HIV viral load in patient receiving GM-CSF by the use of concurrent antiretroviral drugs.[37]

Table 2.8.4: Neutropenia and HIV infection

Decreased production/impaired myelopoiesis
• ***Drugs:*** Zidovudine, Acyclovir, Gancyclovir, Co-trimoxazole, anti-TB therapy
• ***Deficiencies:*** Folate, Vitamin B_{12}
• ***Infection:*** HIV, MTB, CMV, EBV, Mycobacterium avium complex, Histoplasma capsulatum
• ***Neoplasia:*** Non-Hodgkin's lymphoma, Hodgkin's disease
Increased destruction
• ***Autoimmune neutropenia:*** anti-neutrophil antibodies
• ***Hypersplenism:*** infection, hemophagocytosis

The approach to a child with neutropenia includes an assessment of nutritional factors, drugs and a search for opportunistic infections and infections resulting from the neutropenia. Serology and cultures of appropriate specimens sometimes including bone marrow aspirates are indicated. Bone marrow is indicated where the etiology is unclear, when there are other cytopenias, with an unexplained PUO and with suspected malignancy.

Coagulation Abnormalities

There is increased predisposition to thrombosis - up to ~2 percent of patients. Factors associated with venous thromboembolic complications include-advanced disease, presence of CMV or other AIDS defining opportunistic infection, hospitalization, and therapy with the protease inhibitor Indinavir. The risk of thrombosis is also higher with coexisting malignant, inflammatory or autoimmune disorders and vascular damage due to drugs and indwelling catheters.

Hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) occur in HIV infection.[16,38,39] TTP is characterized by fever, thrombocytopenia, microangiopathic hemolytic anemia (MAHA), renal failure and neurological abnormalities. A deficiency or inhibition of ADAMTS-13 is implicated. Treatment is with plasma infusion and/or plasmapheresis. Platelet transfusion may be detrimental and steroids have not shown clear benefit. HUS occurs later in HIV disease and has a worse outcome. The pathogenesis of HUS may be related to toxin production (Shigella dysenteria, *E coli* O157:H7), cytokine production and infection (HIV, CMV).

Antiphospholipid antibodies (lupus anticoagulant) occur in 20-70 percent of patients.[40] These antibodies inhibit factor Va and Xa, calcium and phospholipid and are associated with an increased risk of thrombotic events.

Increased thrombotic events may also occur due to decreased levels of antihrombin III, protein C and proteins.[41] With HIV associated nephrotic syndrome increased levels of coagulation factors (V, VIII, X) and platelet hyperactivity are additional contributory factors for thrombosis.[39]

Apart from thrombocytopenia there may be a bleeding tendency secondary to a deficiency of the vitamin K dependent factors (II, VII, IX and X). Vitamin K deficiency is usually due to an enteropathy and may require correction with Vitamin K.

Case Studies

Case 1

Baby OM was a 2.4 kg female born at term to an HIV positive mom. Mom received only nevirapine and baby received nevirapine and AZT after delivery. She had hepatosplenomegaly at birth with mild purpura.

Full blood count at birth showed Hb 14G/dl, MCV 100 fl, Platelet 88 x 10^9/l and WCC 8.1 x 10^9/l (Absolute neutrophil count 5). The child was started on treatment for suspected intrauterine infection with penicillin and gentamicin and AZT for prevention of mother to child transmission of HIV. The initial thrombocytopenia and petechiae resolved by day 7. HIV infection was confirmed by PCR.

In week 2, the Hb dropped to 7G/dl with polychromasia ++, normal platelets and white cells. The Coombs' test (anti- IgG and anticomplement) was positive (++) and both the parvovirus IgM and CMV IgM were positive. IVIg was administered (total of 5 g over 2 days) and the child was transfused 4 days later due to difficulty in obtaining compatible blood. Prednisone was commenced at 5 mg daily with antifungal prophylaxis.

The child became pale again on day 30 with Hb now 4G/dl. Lab results: Hb 4.0, MCV 100 fl, WCC 12 (Neut 5.0 Lymph 6.5 Mono 0.5) plat 413. Reticulocytes 1.6 percent corrected. Other tests LDH 850U/l; Coombs' +++; bilirubin 22 umol/l.

Rx: Repeat polygam and red cell transfusion; continue steroids (2 mg/kg) daily, folate and IVIg repeated every 2-3 weeks.

Further investigations: CMV PCR positive in bone marrow, blood and urine.

Bone marrow: Some dysplasia, adequate myelopoeisis, serous atrophy present. Parvovirus PCR in marrow was negative.

Child commenced on gancyclovir in the 6th week and Hb continued to drop to <5 G/dl with preservation of the other cell lines and she needed repeat transfusion. ART was also commenced 2 weeks after the ganciclovir.

Baby became Cushingoid with the continuation of the steroids (5 mg/kg) and despite this and the prophylactic IVIg, Coombs' test remained positive (+++ to ++++) and Hb dropped again to <5 G/dl. In addition to polygam and transfusions it was decided to empirically add oral cyclophosphamide 50 mg weekly for steroid sparing. This was administered for 2 months and gradually all treatment modalities were tapered and stopped by 11 months of age.

Some Practice Points

- AIHA can be serious and life threatening; Coombs' testing is nonspecific in many cases but still has significance in the individual patient
- Compatible blood may take some time to obtain and in emergency situations the least incompatible blood must be used
- IVIg is useful (both for immune modulation for AIHA and for therapy for suspected infection like parvovirus)
- A suboptimal reticulocyte response may be due to hematinic deficiency and marrow pathology (parvovirus infection, in our case serous atrophy)
- Multiple etiologies may be present
- An underlying cause for AIHA may need to be treated
- High dose steroids may not be sufficient treatment.

Case 2

SS is an 8-year-old female who was referred for recurrent anemia. She was HIV ELISA positive and had commenced anti-TB therapy 1 year earlier. ART comprising of lamivudine, stavudine and efavirenz was started 10 months earlier. In the preceding 6 months the child needed 6 transfusions of packed cells. Examination showed an undistressed pale child weighing 25 kg with shotty lymphadenopathy and no visceromegaly.

FBC on referral:

- Hb 7.0 G/dl, MCV 83, Plat 388 x10^9/l, WCC 8.96 x10^9/l (N 2.77 L 5.19 M 0.98) Reticulocyte 0.2 percent, corrected 0 percent, Absolute 4.96 x10^9/l.

Other investigations showed:

- Normal liver function tests with an albumin of 36 G/l and bilirubin of 6 umol/l.
- Normal urea and electrolytes.
- Vitamin B_{12}: 1060 pg/ml; Folate: 8.7 ng/ml
- Ferritin 1236 ng/ml Serum iron: 50.4 umol/l; Transferrin: 2.28 g/l; Iron saturation 98 percent.
- CD4 count: 767/ul; CD4 percent: 21.4 percent; Viral load: undetectable.

Bone marrow aspirate and trephine:

- Normocellular; myeloid:erythroid ratio 43:1; adequate megakaryocytes and myeloid precursors; suppressed erythropoeisis with maturation arrest. Iron stores 4/6. No infiltrate present and stains for fungi and TB negative. Parvovirus and CMV PCR negative and TB culture negative.
- A diagnosis of pure red cell aplasia was made with the etiology being most likely drug induced. Co-trimoxazole was stopped and the referring hospital was advised to consider a change in the ART regimen as lamivudine was suspected to be the cause. Erythropoietin was commenced.

- The child continued to drop her Hb and needed further transfusions at the referral hospital. The ART regimen was only changed 5 months later (lamivudine discontinued and abacavir included). Up to this point the child remained transfusion dependent. After the change in the ART regimen there was a gradual recovery and by 4 months there was evidence of red cell recovery. FBC at this stage showed:
  - Hb 12.3 G/l MCV 93.3, WCC 6.65 × 10^9/l (normal differential) Platelet 327 × 10^9/l; Reticulocyte count 2.18 percent, corrected count 1.8 percent, absolute count 88 × 10^9/l.

Practice Points

- Suspect PRCA if repeated transfusions are necessary
- Reticulocyte counts not routinely done and very low counts are the clue
- Main drugs implicated: zidovudine, lamivudine and sometimes cotrimoxazole
- With immune recovery (normalised CD4 counts and low/undetectable viral load) suspect drug etiology
- With immune suppression suspect a parvovirus infection
- Parvovirus PCR is often necessary as the parvovirus IgM is not reliable
- IVIg and ART are needed with the parvo associated PRCA
- High serum iron and iron saturation may be a clue to red cell aplasia
- Erythropoietin is indicated in refractory patients
- Patients tolerate lower Hb better and threshold for transfusion could be 5-6 G/dl.

Case 3

NM is an 11-year-old male who presented initially with generalized lymphadenopathy. He was diagnosed as having HIV infection. His CD4 count was 2000/ul (CD4% = 25%) 3 months earlier and he was being followed up anticipating future ART. He had a dental extraction and began bleeding profusely after the procedure. Mom admitted to easy bruising noted in the past month. There was a tuberculosis contact in the household.

On admission he was noted to have small lymphadenopathy, mild parotid enlargement, dental caries, hepatomegaly 2 cm and a tipped spleen. FBC: Hb 9.5 G/dl, MCV 78, WCC 6.64 (N4.54 L 1.5 M0.4), platelet 4 × 10^9/l. He was given oral tranexamic acid and steroids were commenced at 1 mg/kg with fungal prophylaxis and cotrimoxazole. Sputa were sent for AFB and a Mantoux was performed.

He defaulted and presented one month later with gum bleeding. At this stage the FBC showed: Hb 11.4, MCV 83, WCC 5.7 × 10^9/l (N 3.6 L 1.2 M 0.4 Bands 0.4), Platelet 11 × 10^9/l. Smear showed a normocytic normochromic anemia.

Because of uncertainty regarding response to previous treatment and the presence of TB a bone marrow examination was performed. This showed a normocellular marrow with representation of all cell lines. Dysplasia present. Adequate megakaryocytes. No infiltrate noted; stains for TB and fungi were negative. CMV PCR and TB culture were negative.

Repeat CD4 count was 200 ul (CD4% =6%). The child was recommenced on prednisone at 1 mg/kg daily with cotrimoxazole and fungal prophylaxis. He was also commenced on ART.

Repeat platelet counts normalized within a month and the steroids were tapered and stopped over four weeks. There were no further drops in the platelet count and he was discharged to his nearest ART clinic.

Practice points

- Steroids at 1 mg/kg daily is useful for HIV associated immune thrombocytopenia;
- Prophylaxis for PCP, fungal and TB infections must be considered;
- IVIg is useful with active bleeding but effect is transient;
- In presence of hepatosplenomegaly, underlying TB, CMV or EBV are possible;
- The presence of large platelets or increased mean platelet volume is a clue to "ITP";
- The smear should be examined for evidence of fragmentation;
- A low platelet count following platelet transfusion is not unexpected with immune thrombocytopenia, large splenomegaly and active bleeding;
- Consider a bone marrow to exclude coexisting pathology;
- Delay in initiating ART may be accompanied by delay in platelet recovery;
- Splenectomy is usually not indicated in childhood.

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2.9

Renal Disease in Pediatric HIV Infection

Steven Welch

Introduction

Renal involvement is a relatively under recognized manifestation of HIV infection. A wide variety of factors contribute to renal complications, including HIV itself, advanced immune suppression and immune activation, genetic predisposition, opportunistic and other infections, dehydration, use of nephrotoxic drugs and especially as patients survive longer, comorbidities. Renal disorders in HIV may be classified according to the clinical manifestations, underlying pathology and by direct or incidental involvement of HIV. There is, as usual, some overlap between the clinical presentations of different underlying renal pathologies. Renal biopsy may therefore often be useful to define the exact cause in more severe cases, but may not always be safe or practicable. The number of factors contributing to renal complications of HIV make it very difficult to accurately estimate the incidence of these complications in populations, and impossible to extrapolate incidence rates from one population to another. The two most important variables are probably the effect of Highly Active Antiretrovial Therapy (HAART) on the incidence and type of renal manifestations, the striking racial variation in the incidence of the most specific direct renal complication of HIV, HIV associated nephropathy (HIVAN). HIVAN is found almost exclusively in patients of African origin. All estimates of incidence need to be read in the context of the genetic mix, availability of HAART and developed or less developed country setting of the study.

Renal complications of HIV were described early in the course of the HIV epidemic, in both adults and children, initially in the United States.[1,2] A classification of renal complications of HIV was proposed in 1987 by Rao, based initially on manifestations in adults:[3]

1. HIV associated nephropathy.
2. HIV associated immune complex kidney disease (HIVICK) and other glomerulopathies related to immunological abnormalities (IgA nephropathy, lupus-like syndromes).
3. Acute tubular dysfunction with electrolyte fluid abnormalities and/or renal failure caused by infections and nephrotixc drugs.
4. HIV associated thrombotic microangiopathies, including atypical form of hemolytic uremic syndrome.

To these may be added malignancies and conditions occurring in HIV infected patients unrelated to their HIV, including urinary tract infections. An alternative classification would be by clinical manifestation: Proteinuria, renal failure, hematuria, pyuria, hypertension, abnormal renal endocrine function, tubular disorders, electrolyte and acid-base disturbances.

Understanding of different renal pathologies in HIV has progressed and this chapter will look at renal disorders in HIV classified by underlying cause. Clinical manifestations will be emphasized, and stressed again in later case examples, with a practical approach to case management. Recent advances will also be highlighted.

HIV Associated Nephropathy (HIVAN)

HIVAN is a clinical syndrome of proteinuria with progressive glomerular renal impairment. Proteinuria is often in the nephrotic range and results in hypoalbuminemia, but edema may be relatively limited, presumably because plasma oncotic pressure is partly maintained by the hypergammaglobulinemia of HIV. Hypertension is uncommon, as are macroscopic hematuria, and either microscopic hematuria or renal failure without proteinuria. Ultrasound scan shows hyperechoic, often enlarged kidneys. The characteristic histological pattern on biopsy is of collapsing focal segmental glomerulosclerosis (FSGS) with microcystic tubular dilatation, although mesangial hyperplasia (MH) may predominate, and is more common in children.[4-9]

Epidemiology

HIVAN was first described in 1984 in the US, initially in adults, and subsequently also in children.[1,2] The two

main factors which influence the incidence of HIVAN are advanced HIV infection with low CD4 count, and racial origin. The association with advanced disease is well described.[4-10] A large adult study showed that new onset of HIVAN does not occur in patients well-controlled on HAART with good CD4 counts.[10] HIVAN is a WHO stage 4 or CDC stage C disease, in other words it implies advanced clinical HIV or AIDS. This has given rise to a rather peculiar epidemiological pattern. HIVAN became recognized in European and North American studies as the HIV epidemic progressed, but has become much less common as HAART has decreased the numbers of patients with advanced HIV disease. Conversely, although HIVAN has been described in adults and children with HIV from all areas of the world, the high mortality of patients with advanced HIV has historically resulted in low rates of diagnosis of HIVAN and other renal complications in less developed countries. As HAART becomes increasingly available globally, more patients with HIV are surviving in less developed countries, sometimes with suboptimal virological control. This is likely to result in a rise in the diagnosis of HIVAN and other renal complications, so it will become increasingly important for pediatricians and physicians to recognize these and know how to manage them. This pattern is already becoming apparent in a number of case series from across the world.[6,8,9,11-13]

From the first descriptions in North America, HIVAN was noted to be much more common in patients of African ancestry than in other racial groups.[4,5] Indeed, although proteinuria is described in patients with HIV of all racial origins, it is questionable whether biopsy-proven HIVAN actually occurs in non-African populations.[5,9,11-14] There is, of course, also a great deal of genetic variation between different African populations and if, as predicted, HIVAN becomes more commonly recognized as more patients with HIV in Africa survive longer, it remains to be seen what the distribution of the frequency of HIVAN in different African populations will be.[13]

The most common age of onset of HIVAN in children with vertically acquired HIV infection has been 3-5 years.

Pathophysiology

The pathophysiology of HIVAN is increasingly better understood.[6,9,15-17] It appears to be related directly to HIV infection of renal cells resulting in glomerular proliferation and the characteristic collapsing focal glomerulosclerosis. This is evidenced by its occurrence in the rat kidney model where HIV genes are expressed. However, much remains to be answered. The predominance of mesangial hyperplasia in some children and the association of this with better renal outcome leave an open question of whether MH represents a milder version of the same pathology or a distinct entity.[5,9]

Diagnosis—Need for Biopsy, Pragmatic Response to ART

HIVAN is suggested by the occurrence of renal failure with proteinuria in patients of African ancestry with characteristic ultrasound findings and without significant hematuria, hypertension or edema (Table 2.9.1). Ideally, patients should have a renal biopsy to confirm diagnosis. This may be particularly important as HIV is diagnosed and treated in populations with newly increasing HIV prevalence in whom the incidence and even existence of HIVAN is not clearly defined. Where renal biopsy is not readily available, it may be pragmatic to attempt to exclude other diagnoses and make a clinical diagnosis based on the characteristic clinical findings of HIVAN. Possible future alternatives to renal biopsy are discussed on page 176.

Prognosis and Management

Before the use of HAART the outcome in terms of both survival and renal function was poor. HIVAN has been found to be unresponsive to steroids, and in the pre-HAART era carried a very poor prognosis with progression to end-stage renal failure and high mortality from either renal problems or other complications of advanced HIV infection.[4,5,8,15] ACE inhibitors have been found to show some benefit, but the most important intervention is HAART. Some studies have suggested that HAART will always be sufficient to treat HIVAN and proteinuria.[18] but a large study of 16000 adult patients[10] showed that a proportion of patients do not recover renal function, and the most important predictor of progression to end-stage renal failure despite HAART is the severity of renal damage. This suggests that HAART can only reverse renal damage if it is initiated before a threshold of severity has been reached. This indicates the need for early diagnosis of HIV as the underlying cause of renal disease. It also raises the possibility in future of populations whose HIV has stabilized on HAART but who have chronic end stage renal failure and how most appropriately to manage renal replacement.

HIVICK and other Glomerulopathies Related to Immunological Abnormalities

A number of immunologically mediated renal complications may occur in HIV. These include variations of Ig A nephropathy and lupus-like nephritis, as well as HIVICK which does not conform to other recognized patterns of glomerular injury. Unlike HIVAN, there is a less clear clinical pattern and immunological conditions should be suspected in patients with clinical evidence of glomerulonephritis which do not meet the clinical criteria for HIVAN (Table 2.9.1). Ideally, such a diagnosis should be confirmed with a renal biopsy. Proteinuria and renal

Table 2.9.1: Clinical features of HIVAN[5,9]

Features suggestive of HIVAN	*Features suggestive of non-HIVAN renal disorder*
• Persistent proteinuria (≥ 1+) for more than 2 months in absence of infection • Abnormal urine microscopy • Persistently enlarged echogenic kidneys on ultrasound • African origin • Absence of edema and hypertension	• Macroscopic hematuria • Microscopic hematuria without proteinuria • Elevated urea and creatinine without proteinuria • Impaired renal function in child of non-African origin

failure are less pronounced in HIVICK than in HIVAN, although the CD4 counts may actually be lower.[4,6-9,19]

Acute Tubular Dysfunction with Electrolyte Fluid Abnormalities and/or Renal Failure Caused by Infections and Nephrotoxic Drugs

Other Causes of Renal Failure

Acute renal failure (ARF) may occur in HIV infected children at any clinical stage or CD4 count. ARF is always more likely in children who are clinically unwell with systemic infections or other complications and who are using multiple drugs. Possible causes are listed in Table 2.9.2.[20] HIVAN is an unlikely new cause in patients with a good CD4 count, and general management should focus on identifying and removing exacerbating factors, such as sepsis, hypovolemia and drug toxicity. Biopsy may sometimes be required to exclude HIVICK. Supportive management or short-term renal replacement therapy may be required.

Renal Tubular Function

Renal tubular involvement is well described in HIVAN. Characteristic histological changes in the renal tubule have been described without the glomerular features of HIVAN; it is unclear whether this represents an "incomplete" or early HIVAN, or a separate associated disease process. Studies looking at renal tubular function in HIV are few, but where they have been done show significant abnormality in untreated adults,[21] but not in HAART treated children.[22] Tubular abnormalities may result in renal tubular acidosis and hypophosphatemia. There is an urgent need for studies of renal tubular function in HIV infected patients and for more widely available clinical tests of tubular function.

Table 2.9.2: Causes of acute renal failure in children with HIV[20]

Prerenal	• Fluid losses, e.g. gastrointestinal • Sepsis • Hypotension, e.g. cardiomyopathy • Decreased renal perfusion, e.g. drugs
Renal	• Acute tubular necrosis, e.g. sepsis, ischemia, drugs • Intertitial nephritis, e.g. drugs, infections • Golmerulonephritis, e.g. HIVICK, TTP
Postrenal	• Tubular obstruction, e.g. tumor lysis syndrome, drugs • Extrinsic obstruction, e.g. tumors • Intrinsic obstruction, e.g. stones, fungal balls

Nonspecific Electrolyte Abnormalities

Electrolyte abnormalities are found commonly in HIV infected children in the absence of renal failure. Studies from the US before widespread use of HAART suggested that 25 percent of children developed hyponatremia and the most common cause was Syndrome of Inappropriate Anti Diuretic Hormone secretion (SIADH).[20] This occurs less commonly in the era of HAART and fluid loss and dehydration are much more common cause of hyponatremia globally. In the presence of hypovolemia, a low urinary sodium suggests non-renal fluid losses (e.g. gastrointestinal), whilst a high urinary sodium suggests renal losses (renal salt wasting or diuretics). High urinary sodium without hypovolemia suggests SIADH.[20]

Hyperkalemia may occur without renal failure in adrenal failure or hypoaldosteronism and drugs may cause hypokalemia or hyperkalemia without renal failure.

Abnormal Fluid Balance

Gastroenteritis and sepsis may result in hypovolemia, with or without associated electrolyte abnormalities, acidosis, shock or prerenal failure. Children with advanced HIV have a large number of potential causes of hypovolemia, including chronic diarrhea due to infection or HIV enteropathy, CMV colitis, sepsis, renal problems.

Acid Base Balance

Metabolic acidosis may occur as part of septic shock or renal failure. There may also be chronic diarrhea. ART, especially nucleoside analogues (NRTIs) may cause lactic acidosis. The presence of an increased anion gap in the absence of sepsis or other causes may suggest this.

Drug Toxicities

Antiretrovirals

A wide spectrum of renal side effects of antiretroviral drugs has been described (Table 2.9.3).[23] It should be

Table 2.9.3: Nephrotoxic side effects of antiretroviral drugs

Drug class	*Drug*	*Side effects*
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
	All drugs in class	Metabolic (lactic) acidosis
	Didanosine	Acute renal failure
	Lamivudine	Rhabdomyolysis
	Stavudine	Especially likely to cause lactic acidosis
	Zidovudine	Rhabdomyolysis
Nucleotide Reverse Transcriptase Inhibitors (NtRTIs)		
	Tenofovir	Fanconi syndrome with secondary hypophosphatemia and osteomalacia Increased frequency of renal impairment, especially if baseline renal function diminished
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		No major renal toxicities
Protease Inhibitors (PIs)		
	All drugs in class	Rhabdomyolysis
	Atazanavir	Hypertension Nephrolithiasis Urinary frequency Hematuria, Proteinuria
	Darunavir	Hypertension Dysuria, Polyuria Nephrolithiasis Renal failure Hyponatremia
	Indinavir	Interstitial nephritis Nephrolithiasis Crystalluria Dysuria, Hematuria Proteinuria, Pyuria Pyelonephritis
	Lopinavir	Electrolyte disturbances Hypertension Vasculitis Dehydration Nephritis Hypercalciuria Lactic acidosis Hyperuricemia
	Ritonavir	Electrolyte disturbances Hyperuricemia Dehydration Postural hypotension Renal failure
	Saquinavir	Renal impairment
	Tipranavir	Renal impairment Dehydration
Other antiretrovirals		
	Enfuvirtide	Hematuria Renal calculi
	Maraviroc	Renal failure Polyuria
	Raltegravir	Renal failure

remembered that overall, the use of ART greatly improves renal function in HIV infected populations by reducing the risk of infections leading to sepsis, dehydration and exposure to other nephrotoxic drugs, as well as the risk of direct HIV related renal complications. The risk of renal toxicity from ART is also greater in patients who are unwell than in stable patients whose HIV is well controlled on therapy. Most of the complications listed in Table 2.9.3 are uncommon, but a few have been important and merit further consideration.

The association of use of the protease inhibitor indinavir with crystalluria and sometimes more significant nephrolithiasis, interstitial nephritis and renal failure is important because it was the first well described clear link between an ARV drug and a specific significant renal side effect. The importance of this is now largely historical as indinavir has been superseded by newer protease inhibitors.

Lactic acidosis is a rare but potentially life-threatening complication of NRTIs. It may occur with any drug in the class, but does appear to be less common with newer drugs than older drugs such as stavudine. However, it is important to bear this in mind as part of the differential diagnosis in any patient exposed to NRTIs who presents with a severe metabolic acidosis, including infants exposed to NRTIs *in utero* or postnatally as part of prevention of Mother to Child Transmission (PMTCT) programs. Metabolic acidosis is much more commonly due to sepsis and may be renal in origin. These causes need to be actively sought to determine whether it is riskier to stop or continue NRTI use.

The biggest debate currently surrounds the relative renal safety or toxicity of tenofovir. This nucleotide analog reverse transcriptase inhibitor is becoming increasingly widely used in adult drug regimens worldwide and although unlicensed in children, is also used by pediatricians. Although many patients use tenofovir without adverse effects, there is a risk of developing decreased renal function, which appears to be greater in patients with pre-existing renal impairment. Probably more common than renal failure is an effect on renal tubular function, which may include renal losses of phosphate and consequent decreased bone mineralization. This may be more significant in children with immature skeletal development than in adults. It is not yet apparent what is the best way to screen patients before tenofovir use and to monitor them whilst on the drug.[24] There is also an urgent need for safety data on tenofovir use in children.

The balance between long-term drug toxicities and effects of chronic HIV infection will be discussed again on page 176.

Other Drugs Used in HIV

Many other drugs used commonly in HIV, including those used to treat and prevent opportunistic infections, may affect renal function (Table 2.9.4). These drugs are most likely to be used when the patient is unwell and more susceptible to renal compromise. The potential for antibiotics and especially aminoglycosides, to cause renal impairment should always be considered when renal function deteriorates acutely in children being treated for opportunistic or other intercurrent infections. Most non-ART antivirals, but especially cidofovir, can be nephrotoxic. Many antifungal drugs are primarily hepatotoxic, but amphotericin commonly affects the kidney and the frequency with which cotrimoxazole is used to treat or prevent Pneumocystis infection in HIV makes its renal toxicity important. Table 2.9.4 contains the most important and common drug side-effects, but is not exhaustive, and a thorough history of current and past drug usage including herbal and over-the-counter medications, should always be part of the assessment of renal impairment.

Drug Modifications in Renal Failure

Most NRTIs and some PIs are excreted by the kidneys and therefore dose adjustments may be required when using these drugs in patients with impaired renal function. NNRTIs are largely metabolized in the liver, and do not require dose adjustment. Of the newer classes of ARVs currently licensed, only maraviroc is likely to require dose modification. The level of decreased creatinine clearance at which dose modification is likely to be required for each drug is given in Table 2.9.5. Details of the dose modification required should be obtained from the product literature.

Table 2.9.4: Nephrotoxic side effects of non-ARV drugs commonly used in HIV infection

Drug class	*Drug*	*Side effects*
Antibiotics	Aminoglycosides	Acute renal failure Hypomagnesemia
	Cotrimoxazole	Hyperkalemia Hyponatremia Interstitial nephritis
	Penicillins	Interstitial nephritis
	Rifampicin	Acute renal failure
Antivirals	Aciclovir	Renal impairment
	Cidofovir	Severe renal impairment
	Foscarnet	Renal impairment
	Ganciclovir	Renal impairment
Antifungals	Amphotericin	Hypokalemia Hypomagnesemia Renal failure
	Pentamidine	Hypotension Acute renal failure

Table 2.9.5: Dose adjustments of antiretrovirals in renal impairment

Drug class	*Drug*	*Side effects*
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
	All drugs in class	Use with caution in renal impairment
	Abacavir	Manufacturer advises avoidance in end-stage renal failure
	Didanosine	Reduce dose if creatinine clearance <60 ml/minute
	Emtricitabine	Reduce dose if creatinine clearance <50 ml/minute
	Lamivudine	Reduce dose if creatinine clearance <50 ml/minute
	Stavudine	Reduce dose if creatinine clearance <50 ml/minute
	Zidovudine	Reduce dose if creatinine clearance <10 ml/minute
Nucleotide Reverse Transcriptase Inhibitors (NRTIs)		
	Tenofovir	Interrupt treatment if renal impairment progresses Reduce dose if creatinine clearance <50 ml/minute
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
	Efavirenz	Use with caution in renal impairment
	Nevirapine	No dose adjustment required
Protease Inhibitors (PIs)		
	Amprenavir	Avoid use of oral solution in renal failure and use with caution in renal impairment
	Atazanavir	No dose adjustment required
	Darunavir	No dose adjustment required
	Fosamprenavir	No dose adjustment required
	Indinavir	Avoid in renal impairment
	Lopinavir	Use with caution if creatinine clearance <10 ml/min Avoid use of solution in renal impairment
	Nelfinavir	No information available
	Saquinavir	May need dose adjustment if creatinine clearance <10 ml/min
	Tipranavir	No dose adjustment required
Other antiretrovirals		
	Enfuvirtide	No dose adjustment required
	Maraviroc	May need dose adjustment if creatinine clearance <80 ml/min
	Raltegravir	No dose adjustment required

Microangiopathies

In HIV uninfected patients, thrombotic thrombocytopenic purpura (TTP) occurs primarily in adults, and hemolytic uremic syndrome (HUS) primarily in children, often secondary to Shiga-toxin producing diarrheal organisms such as *Escherichia coli* 0157:H7. Both disorders are thrombotic microangiopathies and are characterized by thromocytopenia, microangiopathic hemolytic anemia and elevated lactate dehydrogenase (LDH). The microangiopathy in HUS is due to endothelial injury and results in severe renal failure associated with hyperkalemia, oliguria, fluid retention and hypertension. Renal failure in TTP may be milder than in HUS and is associated with neurological abnormalities. The microangiopathy in TTP occurs due to platelet aggregation resulting from decreased activity of the von Willebrand factor-cleaving protease known as ADAMTS-13. ADAMTS-13 activity may also be decreased in atypical (D-, nondiarrhea-associated) HUS.

TTP is known to occur more frequently in HIV infected adults and both TTP and atypical HUS have been described in children with HIV. Microangiopathies are also described in post mortem and renal biopsy series in HIV infected children.[9,25,26] Both TTP and HUS are medical emergencies which may be treated successfully with plasmapheresis and supportive renal care, and the availability of ARVs means that the long-term prognosis can be good after treatment of the emergency. A diagnosis of TTP or HUS needs to be considered in any child presenting with renal impairment and thrombocytopenia, prompting examination of a blood film to identify microangiopathic hemolysis and allow correct treatment to be instituted. Conversely, renal specialists not used to looking after HIV need to be made aware of the need to test for HIV in children (and adults) presenting with TTP or atypical HUS.

Others

UTI, Stones, Tumors, Comorbidities, Renal Infections

There is no evidence of any increase in the incidence of urinary tract infection (UTI) in children with HIV infection, but because UTIs are common in childhood they may be seen in children with HIV.[12]

Vasculitis may occur in association with HIV resulting in renal involvement.

Nephrolithiasis was described in indinavir use, but this is otherwise uncommon.

Other than in end-stage renal failure, there is no well described effect of HIV on renal endocrine function. Many population studies find an association between HIV and vitamin D deficiency, but this is likely to be due to general deficiency rather than a defect in renal hydroxylation.

Tumors occur less frequently in children than adults with HIV, but renal and urinary tract tumors have been described. Renal failure may also occur due to tumor lysis syndrome from nonrenal tumors.

Glomerulonephritic disorders which are not thought to be associated with HIV may occur coincidentally in patients with HIV, especially in populations with very high HIV prevalence. Membraneous glomerulopathy, post-infectious diffuse proliferative glomerulonephritis, IgA and IgM nephropathies, non-HIVAN FSGS, membranoproliferative gomerulonephritis, minimal change disease, lupus nephritis have all been described.[9]

A number of factors which may be epidemiologically associated with HIV may result in renal disorders, including malaria, syphilis and hepatitis B; in adult series heroin use may be associated and indeed HIVAN was initially thought to be possibly drug-related; its occurrence in children with HIV but no other problems was an early indicator that this was in fact, primarily HIV related.

Long Term Effects of HIV, HAART and Co-morbidity

As HAART becomes more widely available and patients with HIV survive longer, the effects of chronic HIV infection, long-term use of HAART and comorbidities with aging are becoming more important. It has long been debated whether survival benefits of HAART in reducing AIDS-related mortality will be partially offset by long-term cumulative drug toxicities, including renal damage. The SMART study in adults[27] has answered this question for the medium term, clearly demonstrating that, perhaps surprisingly, non-AIDS related cardiovascular and malignant mortality are also reduced by HAART in the medium-term, increasing enthusiasm for earlier use of HAART. However, although renal-related mortality was reduced with more aggressive use of HAART in SMART, the frequency of grade 4 renal adverse events was increased. Long-term effects of HAART include dyslipidemia and diabetes, which may affect renal function. Although all-cause mortality is clearly reduced by earlier use of HAART, it remains to be seen what the long-term effects of this will be on the incidence of renal disease, which in an aging adult population may increasingly comprise more familiar diabetic and hypertensive nephropathies rather than the conditions described in this chapter. These effects will not be seen in children, but may arise many years later from the treatment decisions made by pediatricians much earlier in a patient's life. These concerns should not detract from the overall spectacular success of HAART in children.

Use of Urinary Biomarkers

Renal biopsy is an important tool in the accurate diagnosis of HIVAN and other renal complications of HIV, but it is not without risk and is not always practicable. Recent work has focused on the possible use of urinary biomarkers, especially iron-related proteins, in the diagnosis of HIVAN.[28] A diagnostic test to replace biopsy is not yet available, but future work with the potential for reducing the need for biopsy is an exciting development.

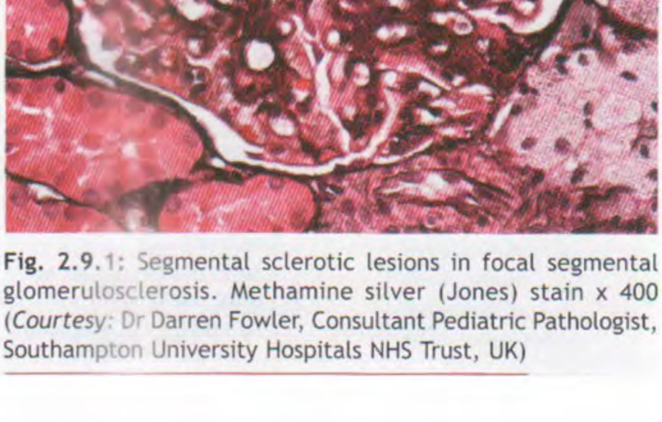


Fig. 2.9.1: Segmental sclerotic lesions in focal segmental glomerulosclerosis. Methamine silver (Jones) stain x 400 (*Courtesy:* Dr Darren Fowler, Consultant Pediatric Pathologist, Southampton University Hospitals NHS Trust, UK)

Genetics and Pathophysiology

Despite advances in the understanding of pathophysiology, much remains to be understood. The mechanisms by which HIV might infect renal cells and how viral protein expression causes glomerular proliferation and the associated tubular damage remain to be answered.[17] Patients of African origin with HIVAN have an increased incidence of other renal conditions in non-HIV infected family members, suggesting that the genetic component may represent an inherited vulnerability of the kidney to a variety of insults. Candidate genes have been suggested, but the exact mechanisms of genetic predisposition still need to be fully understood and the exact frequencies of such genes in different populations need to be determined.

Renal Replacement Therapy and Transplantation

The fact that HAART does not reverse HIVAN if started too late, the increasing survival of children and adults with HIV globally because of increased availability of HAART and in adults, the increase in long-term toxicities of HAART, chronic HIV infection and comorbidities of aging will all result in increased numbers of patients whose HIV is stable and well-controlled, but who may have end-stage renal failure. Published data show that long-term renal replacement therapy can be successfully undertaken in children and adults;[29] renal transplantation has been successfully undertaken in adults, but there are no published data in children.[30] In the era of HAART, HIV is not an absolute contraindication to long-term renal replacement therapy or renal transplantation.

Case Studies

Case 1

A 5-year-old boy is newly diagnosed with HIV, having presented with failure to thrive. His urine dipstick shows proteinuria ++++.

1.1. What clinical features and investigation results do you need to know in order to make a diagnosis and plan management?

1.2. Which clinical features make a diagnosis of HIVAN likely?

1.3. You suspect a diagnosis of HIVAN-based on clinical criteria. How will you confirm your provisional diagnosis?

1.4. How will you manage the child whilst awaiting biopsy confirmation?

Answers

1.1. Has the child had any previous history of renal disorders? Is there a family history? What is his racial origin? Is there any history of disorders which may reduce renal perfusion, such as chronic diarrhea or poor cardiac function? Does he have dysuria or abdominal pain? What is his urine output? A detailed drug history should be taken.

Is there any clinical evidence of current bacterial or opportunistic infection? What is his blood pressure? Are there any abdominal masses?

Urinalysis by dipstick, microscopy and culture should be performed to look for evidence of hematuria, pyuria or renal casts, and for bacterial or fungal urinary tract infection. Renal function should be assessed by measuring serum urea, electrolytes, creatinine, phosphate and a blood gas. A full blood count and film will show if there is thrombocytopaenia or evidence of microangiopathic hemolytic anemia. Baseline plasma HIV viral load and CD4 count and percentage will be needed to plan antiretroviral therapy, and to assess the likelihood of HIVAN and HIVICK, which usually occur at low CD4 counts. An abdominal ultrasound will show any postrenal obstruction and assess the size and echogenicity of the kidneys.

1.2. This child was of African origin, and had no evidence of current bacterial or opportunistic infection. He had not been given any nephrotoxic drugs. Blood pressure was normal, and he had minimal edema and no abdominal pain or masses. He had impaired renal function, with a creatinine of 250 micromol/L and urea of 13 mmol/L. Sodium and potassium were normal, with no acidosis. Platelet count was normal, and he was anemic with a hemoglobin of 10 g/dL, but no evidence of hemolysis. Baseline viral load was 80,000 copies /mL and CD4 count 90 cells /mm^3, 7 percent of total lymphocyte count. Renal ultrasound showed enlarged hyperechoic kidneys. These clinical features are highly suggestive of HIVAN.

1.3. A renal biopsy is desirable to confirm typical findings of focal segmental glomerulosclerosis. If renal biopsy is not deemed practicable and safe, a presumptive diagnosis can be made and response to ART observed. HIVAN has not been commonly described in patients of non-African origin, but large series of biopsy-investigated cases have not been published from some racial groups.

1.4. Supportive treatment should include careful attention to fluid management, electrolytes and monitoring of any acidosis. Potentially nephrotoxic

drugs should be avoided. Renal replacement therapy should be initiated if clinically indicated.

This child needs to start ART anyway on the basis of his CD4 count, and HIVAN is an AIDS-defining condition, CDC clinical stage C, WHO stage 4. Renal impairment reversed in this child on an ART regimen comprising abacavir, lamivudine and efavirenz. Use of an ACE-inhibitor may be considered if there is no rapid improvement in renal function, and renal replacement therapy should be used if appropriate.

Case 2

A 10-year-old girl with known HIV infection presents unwell, with a tachycardia of 150/minute, mild respiratory distress, tachypnea of 40/minute and fever of 38.5°C. Her blood tests show a sodium of 135 mmol/L, potassium 5.0 mmol/L, urea 16 mmol/L and creatinine of 280 micromol/L. You know that she was diagnosed with asymptomatic HIV aged 5 years, when she was tested after her mother was found to be HIV positive in a subsequent pregnancy. She started antiretroviral therapy 2 years ago due to a falling CD4 count, with a regimen of zidovudine, lamivudine and lopinavir/ritonavir. Her adherence is suboptimal, and her most recent HIV viral load 2 months ago was 8000 copies/ mL, with a CD4 count of 280/mm^3 (18% of total lymphocyte count).

2.1. What are the possible causes of acute renal impairment in this girl?

2.2. What further information from history, examination and investigations will help in your diagnosis?

2.3. How should you manage this girl's renal impairment?

Answers

2.1. Likely causes of acute renal impairment in this girl include renal hypoperfusion secondary to sepsis or hypovolaemia from gastrointestinal fluid losses, and drug toxicity. New appearance of specific HIV related renal impairment from HIVAN or HIVICK are unlikely at this CD4 count, but may have occurred if she has stopped taking her ART altogether and her CD4 count has fallen rapidly since last measured; other immunologically-mediated causes of glomerulonephritis, and microangiopathies are also possible, but less likely. New severe opportunistic infections are unlikely at the most recent CD4 count, but should again be considered if she has stopped taking ART. Postrenal obstruction from a new tumor or fungal infection is also a remote possibility.

2.2. It is important to ask whether the girl has stopped taking her ART, as this will broaden the most likely alternative diagnoses. It should be established whether she has recently or repeatedly taken any other medication, including treatment for the current symptoms. Has she had any recent diarrhea or vomiting contributing to hypovolemia?

Examination should look for features of significant intercurrent infection, including septicaemia, pneumonia or meningitis. Abdominal palpation should examine for any masses which may be causing obstruction. Blood pressure should be measured, and evidence of any compromise in cardiac function sought.

Investigations should include urinalysis by dipstick, microscopy and culture, which may help in the diagnosis of glomerulonephritis, or fungal or bacterial infection of the urinary tract. Blood cultures should be performed, and sputum or CSF examination as appropriate according to clinical findings. A full blood count and film should be examined for evidence of thrombocytopaenia or haemolysis, and a blood gas will give evidence of acidosis secondary to the renal impairment. Imaging by chest radiography or abdominal ultrasound may be appropriate if pneumonia or abdominal mass are suspected clinically.

2.3 In this instance, the girl and her family denied having stopped her ART, and this was borne out by the viral load and CD4 results when they subsequently became available a few days later, showing no significant change. She had no diarrhea, but had vomited once to twice daily during the preceding 4 days, and had drunk less than normal. She had taken some non-steroidal anti-inflammatory drugs during the last few days because of her fever, and she had been given an intramuscular dose of gentamicin and some oral penicillin by her general practitioner the day before attending hospital.

Clinical examination revealed no evidence of septicemia or meningism, and there were no palpable abdominal masses. There was decreased air entry in the right lung base, with some crepitations and bronchial breathing. Blood pressure was 104/70.

Urinalysis showed proteinuria +, with no hematuria and no bacteria or fungal hyphae on microscopy. Full blood count showed a leukocytosis with neutrophilia, and normal hemoglobin and platelet counts. Blood gas was normal. Chest radiography showed right lower lobe consolidation. Sputum and blood cultures were sterile.

This girl had a community-acquired right lower lobe pneumonia, with no organism identified, but *Streptococcus pneumoniae* a likely cause. A number of factors are likely to have contributed to her acute renal impairment, including hypovolemia secondary to vomiting, reduced fluid intake and pneumonia, as well as the use of NSAIDs and gentamicin, and a possible predisposition to renal impairment in acute infection due to her underlying HIV. Such a multifactorial cause with no single identified cause is relatively common. Management consisted of

treatment of the pneumonia with intravenous cefotaxime, and careful attention to rehydration guided by clinical assessment of intravascular volume, and measurement of urine output and serial creatinine. Care should be taken to avoid giving further doses of nephrotoxic drugs during the acute illness.

In this instance, the renal impairment reversed with such supportive management, but if it had continued to deteriorate the institution of renal replacement therapy would have been appropriate.

CASE 3

A newborn infant presents aged 14 hours with shock, metabolic acidosis and renal impairment. His mother had been diagnosed with HIV infection during this pregnancy, and received zidovudine, lamivudine and ritonavir-boosted lopinavir during the pregnancy. The mother's HIV viral load was undetectable immediately prior to delivery. The infant received his first dose of zidovudine half an hour after birth.

Examination findings and investigations show: Child is mottled with poor skin perfusion. Heart rate 200/min, respiratory rate 70/min with no respiratory distress, no heart murmur audible. Arterial pH 7.04, pCO_2 7 kPa, pO_2 9 kPa, base excess – 19 mmol/L. Sodium 140 mmol/L, potassium 4.1 mmol/L, creatinine 200.

3.1. How may this child's intrauterine and postnatal drug exposure be related to his presentation? What is the differential diagnosis?
3.2. What investigations should be performed?
3.3. Should this child continue on zidovudine?

Answers

3.1. Nucleoside analogues may cause lactic acidosis secondary to mitochondrial toxicity, and this may occur at birth following intrauterine exposure. However, common neonatal complications, such as sepsis or congenital heart disease are much more common, and likely to be the cause in this infant.

3.2. Investigations (and management) should be aimed at establishing alternative causes, so usual investigations such as blood cultures, lumbar puncture (if child stable enough), and echocardiography are by far the most important to establish the diagnosis. Calculating an anion gap may be helpful, as this will be elevated in lactic acidosis, but will not establish the cause of this.

Treatment should be directed at common underlying causes, so should include immediate antibiotic therapy and supportive intensive care management.

3.3. In this instance, the risk of perinatal HIV infection is small as the mother's HIV viral load was undetectable. It is therefore reasonable to stop the zidovudine, even if this is unlikely to be the cause of acidosis, as the likely benefit from continuing zidovudine is low. If the mother's viral load were higher, and the infant needed treatment to reduce the risk of congenital infection, or for treatment of established infection, the relative risks would have to be weighed up. In these circumstances, it would be particularly important to establish or exclude alternative diagnoses rapidly, and alternative classes of antiretrovirals (such as lopinavir/ritonavir and nevirapine) might be used in the immediate term until the safety of continuing NRTIs had been established. If NRTI toxicity were likely to be the cause, treatment would comprise stopping the NRTIs and providing supportive treatment.

In this instance, zidovudine was discontinued, and blood cultures rapidly established a diagnosis of early-onset group B streptococcal septicemia, which proved fatal despite maximal intensive care.

Key Messages

- Unusual renal problems may be the first manifestation of HIV infection and the diagnosis should be considered and an HIV test performed, in children who present, amongst others, with complicated proteinuria and renal failure, atypical HUS, TTP or an immune-mediated glomerulonephritis.
- The relative incidence of HIVAN in genetically varying African populations and the existence of HIVAN in non-African populations with rising HIV incidence, need to be established. All efforts should be made to make an accurate diagnosis of the etiology of renal complications in children with HIV infection, including renal biopsy where practicable.
- Drug toxicity should always be considered in HIV infected children with renal complications. As the use of tenofovir increases globally, there is an urgent need for data on its renal safety in children and for data on how best to monitor renal function, including tubular function, in patients taking this drug.
- In the era of HAART, a diagnosis of HIV is not an absolute contraindication to long-term renal replacement therapy, nor to renal transplantation in adults. Data on renal transplantation in HIV infected children are awaited.

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2.10

Gastrointestinal and Hepatobiliary Manifestations in Children with HIV

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Introduction

Today, more than 25 years after the description of the first AIDS cases in children, major advances have been made on the prevention and treatment of the infection caused by Human Immunodeficiency Virus (HIV-1), mainly after the availability of Highly Active Anti Retroviral Therapy (HAART). Despite improved access to antiretroviral treatment and prevention, the HIV epidemic continues to expand. Although the proportion of pregnant women and children who receive antiretroviral treatment is increasing, it is still insufficient, resulting in a high incidence of infection in children in developing countries. In 2008, around 2.1 million children are thought to be infected with HIV worldwide and every day it is estimated that nearly 1200 children are newly infected with the virus, in whom mother to child transmission is the predominant mode of infection. In addition it is estimated that there are 14 million orphan children as a consequence of HIV infection in their parents.[1] The progression of the disease is much faster in children than in adults as well as the risk of complications. HIV infected infants frequently present with clinical symptoms in the first year of life. A large metaanalysis of 7 African studies done to assess interventions to prevent vertical transmission have shown that around 50 percent of HIV infected children die by the age of 2 years, without antiretroviral treatment.[2]

The gastrointestinal (GI) tract is a major organ involved in HIV infection. The GI tract is a major target for HIV because it constitutes 60 percent of all lymphoid tissue in the body.[3] During the initial infection with HIV, heavy involvement of Gut Associated Lymphatic Tissue (GALT) leads to a rapid and probably permanent destruction of lymphoid tissue.[4] The presence of HIV has been demonstrated in the mucosa of small intestinal and colonic biopsy specimens from patients with HIV.[5] In addition, the GI tract may be the portal of entry of the virus. The newborn may swallow blood and vaginal secretions from the mother during delivery that may lead to infection. In developing countries HIV infection commonly occurs from mother to child through breastfeeding. In sub-Saharan Africa, HIV-1 acquisition through breast milk accounts for more than 40 percent of infections in children.[6] There has been well documented transmission through some practices of feeding done in some parts of the world such as food premastication from an HIV infected adult to infants.[7]

Worldwide, gastrointestinal disease continues to account for a high proportion of presenting signs and symptoms of HIV infected children. Before the advent of HAART, most estimates suggested that 50 to 93 percent of the patients with HIV disease present with significant GI complaints during the course of illness. Initial descriptions of HIV infection termed the wasting and gastrointestinal disorders as "slim disease" and is still how the disease is called in many parts of the world. Early in the epidemic, chronic diarrhea was recognized as a hallmark of advanced HIV infection, especially in developing countries. A dysfunctional GI tract can produce significant clinical symptoms that contribute to morbidity and mortality in children with HIV infection. Children infected with HIV are subject to a number of GI disorders, which often result in malnutrition and failure to thrive, further compromising an already impaired immune system. Enteric infections represent a major part of GI disease in HIV infected children and may be a source of considerable morbidity and mortality. Diarrheal disease is known to be a leading cause of illness and death in HIV infected children in Africa.[8,9] Hepatobiliary disease is also common in children in the absence of HAART both as a manifestation of opportunistic infections and a result of viral coinfections. In addition, both GI and hepatobiliary associated toxicities are common adverse events of many antiretroviral agents. Although, the development of antiretroviral agents has improved in recent years, it is delayed in children compared to adults, in as much as specific pharmacokinetic studies are needed across all age groups and palatable and suitable formulations are

required in children. Even with these shortcomings, 17 antiretroviral agents have been approved by the FDA in children at different ages. Toxicities associated with antiretrovirals in children may be both individual or class-related, GI and hepatobiliary systems being the most frequently involved.

Epidemiology

In countries with a high prevalence of HIV infection, HIV and malnutrition are closely linked. Many parallels exist in the immune function of children with protein calorie malnutrition (PCM) and children with HIV. Because most children with HIV also experience nutritional deficits, malnutrition is considered a cofactor of immune dysfunction and may contribute to explain the more severe course of children in developing countries in the natural history of the disease. The so called "vicious cycle of PCM, infection and immunity" is frequently triggered by HIV in children. Before the advent of HAART and in countries where it is not widely available, 90 percent of HIV infected children experienced wasting and/or nutritional deficits during the course of their disease. Multiple factors are responsible for malnutrition in HIV infected children, including anorexia, dysphagia, abdominal pain, diarrhea and hepatobiliary disorders caused by the virus itself or by HIV associated infections and HIV associated diseases.

Even though the introduction of HAART has significantly decreased mortality in HIV-1 infected adults and children,[10,11] there is still an increased risk of death compared to the general population, particularly in those children with low CD4 and AIDS-defining illness at entry.[12] Nevertheless, HAART has dramatically changed the spectrum of the disease. Although the number of opportunistic infections (OIs) has substantially decreased during the HAART era, HIV associated OIs and other related infections continue to occur among HIV infected children.[12] In a recent study in the USA, the proportion of deaths due to OI declined from 37 percent in 1994-1996 to 24 percent after 2000, when HAART was widely available. A greater decline was noted for deaths due to *Mycobacterium avium complex* and cryptosporidium diarrhea.[13] Current WHO guidelines recommend initiating antiretroviral treatment in the first 24 months of age in developing countries,[14] because early treatment is associated with a lower mortality and slows down the progression of the disease.[15] Gastrointestinal complications have fallen dramatically both in adults and children since the introduction of HAART. Therefore, an early identification and close follow up of children born to HIV infected mothers are mandatory to ensure a correct diagnosis of HIV, initiate prophylaxis of HIV associated infections and offer antiretroviral treatment. All HIV infected children should be diagnosed before the development of clinical signs or symptoms. Although the positivity of HIV serology cannot discern the maternal or own origin of the antibodies in the first 18 months, a negative serology rules out the infection in this period if at least 6-8 weeks have elapsed since the cessation of breastfeeding. If feasible, WHO recommends determination of PCR at 4-6 weeks after birth and confirmation of HIV serology at 18 months.[14]

The causes of deaths have also shown a dramatic shift away from AIDS related causes. In adults, more than 50 percent of deaths in HIV infected patients are not related to AIDS, whereas before HAART, more than 90 percent of deaths were AIDS-related.[16] Moreover, as patients are living longer, other infections have assumed more importance in the prognosis, as has been well documented with viral hepatitis in coinfected adults. Improvement in the immune system after the introduction of HAART, even in the absence of complete viral suppression, may serve as prevention and therapy for many AIDS-defining OIs, particularly those lacking effective therapy such as cryptosporidiasis and microsporidiasis.[17,18] Nevertheless, although the prevalence of OIs, AIDS-related illnesses and complications have declined dramatically, it seems that adult patients infected with HIV on HAART are now suffering from more HIV related chronic illnesses including hepatic, cardiovascular and pulmonary diseases.[14]

Drug-induced Side-effects

Although antiretrovirals for HIV has been in use since 1987, the widespread use of HAART has produced an increase in adverse drug reactions. This is a new challenge as many of the adverse drug reactions attributable to antiretrovirals may be indistinguishable from nondrug related illnesses. With the immune boost achieved shortly after the initiation of HAART, a new immune reconstitution syndrome has emerged. The so called Immune Reconstitution Inflammatory Syndrome (IRIS) has been less well characterized in children than in adults.[18] In settings where the prevalence of OIs is high and where HAART is initiated with more severe immunosuppression, the incidence of IRIS is higher than in developed countries. In a study of 153 symptomatic children in Thailand with CD4 below 15 percent at initiation of therapy, the incidence of IRIS was 19 percent with a median time of onset of 4 weeks.[20] Typically these presentations occur between 2 and 6 weeks after the introduction of HAART, but may occur up to 7 months later. This syndrome consists of an exacerbation of signs and symptoms associated with the underlying disease, of infectious and non-infectious etiology, resulting in an apparent clinical worsening. IRIS results from a rapid rebound in immune function that responds to a variety of clinically occult or latent infections that were present

at the time of initiation of HAART, not previously recognized by a previously severely dysfunctional immune system. Abdominal complaints are very frequent, such as abdominal pain, hepatosplenomegaly or abdominal masses, representing inflammatory reactions, usually lymphadenopathies. Generally, high fever is also present and may be prolonged. Likewise a boost in the immune system may be associated with a flare of aminotransferases, that may be due to hepatitis C (HCV) or B virus coinfections (HBV). HBV has been associated with fulminant liver failure. Therefore, recognition of these reactions are of utmost importance and has prompted appropriate screening for hepatitis B virus in those children undergoing HAART.[18]

Antiretrovirals are difficult to manage in children because of complex dosing and the need for continuous adjustment of dosing as the child grows, requiring strict monitoring and permanent adherence to avoid drug resistance.[21] Furthermore, many antiretrovirals, particularly when used combined, have significant side effects and toxicities. Even minor side effects influence patient and family adherence and should be addressed to avoid discontinuation. Adverse effects overlap drug classes and it is more important to recognize and manage potential complications than to focus narrowly on adverse events known to occur from a given class. Diarrhea is common with most antiretrovirals, mainly with the protease inhibitors (PI). With nelfinavir, most children develop mild diarrhea, that is usually quite well tolerated, but occasionally require antiperistaltic agents, such as loperamide, for alleviating the symptoms. With the boosted PI, mild diarrhea is also common, particularly in the first weeks since the initiation.[22] With lopinavir/ritonavir less frequent loose stools have been reported after switching from the old soft-gel capsules to the new tablets.[22,23] Tipranavir boosted with double dose ritonavir has also been associated frequently with diarrhrea and increased aminotransferases in children.[24] The new boosted PI darunavir is better tolerated with a good safety profile, diarrhea being unusual.[24]

Most side effects are not life-threatening but some patients who initially have benign presentations can progress to severe complications. Meticulous care must be taken to assess whether stopping part or all of the antiretrovirals is needed. Consideration should by given to the fact that patients who miss only a few doses of one or more of their medications even for a short period of time may develop viral resistance. In addition, the different half-lives of the antiretrovirals must be taken into account if discontinuation of an antiretroviral is being considered, particularly the non-nucleoside reverse transcriptase inhibitors (NNRTI), in order to prevent residual plasma levels with a non-suppressive regimen that may lead to the selection of resistant mutants.[26]

Hepatotoxicity occurs with almost all classes of antiretrovirals, ranging from asymptomatic transaminase elevations to fulminant hepatic failure. About 5 to 10 percent of patients have increased liver enzyme levels after the initiation of antiretrovirals, with fewer cases in children than adults progressing to severe hepatotoxicity. Although most hepatobiliary abnormalities resolve with cessation of the inciting drug, in most cases withdrawal of the drug is not necessary. Most of the antiretrovirals, particularly the PI and NNRTI, are metabolized by the liver and the cytochrome P450 enzyme system. Hepatotoxicity resulting in hepatocellular damage may occur as a direct effect of the parent drug or via accumulation of toxic metabolites. Various genetic changes, drug interactions and gene polymorphisms in the P450 system may significantly alter a patient's susceptibility to damage from a drug.

It is often difficult to determine whether hepatic injury is a direct medication side effect, drug-drug interaction, or unrelated to medications. Hepatic injury from antiretrovirals is usually mild and transient, but may result in long-term liver damage with jaundice, cirrhosis and fulminant hepatic failure.[26] Table 2.10.1 provides a quick reference to the antiretrovirals found in each class and some associated metabolic and hepatobiliary complications.

Table 2.10.1: Antiretroviral drugs and associated metabolic and hepatobiliary adverse effects

Medication class	*Associated adverse effects*
1. NRTI (Nucleoside Reverse Transcriptase Inhibitors)	
Abacavir	
Didanosine	Hepatotoxicity
Emtricitabine	Hepatic steatosis
Lamivudine	Pancreatitis
Stavudine	Lactic acidosis
Tenofovir	Hypersensitivity syndrome
Zalcitabine	
Zidovudine	
2. NNRTI (Non-Nucleoside Reverse Transcriptase Inhibitors)	
Delavirdine	Hepatotoxicity
Efavirenz	Hepatic necrosis
Etravirine	Hypersensitivity syndrome
Nevirapine	
3. Protease Inhibitors	
Amprenavir	Hepatotoxicity
Atazanavir	Hyperbilirubinemia
Darunavir	Pancreatitis
Fosamprenavir	Dyslipidemia
Indinavir	Hyperglycemia-insulin resistance
Lopinavir/ritonavir	Lipodystrophy
Nelfinavir	
Ritonavir	
Saquinavir	
Tipranavir	

Contd..

Contd..

4. Integrase Inhibitors	
Raltegravir	Hepatotoxicity Hypersensitivity syndrome
5. Entry Inhibitors	
a. Fusion inhibitors	
Enfuvirtide (T-20)	Injection site reactions Hepatotoxicity Hypertriglyceridemia Hypersensitivity syndrome
b. CCR5 coreceptor antagonists	
Maraviroc	Hepatotoxicity Hypertriglyceridemia Hypersensitivity syndrome

Antiretrovirals are believed to cause hepatotoxicity via four mechanisms: direct drug toxicity, hypersensitivity reactions, mitochondrial toxicity and immune reconstitution. They can present with signs of hepatocellular damage, a cholestatic pattern, or a combination of both. Hepatocellular injury is direct hepatocyte damage that is often reflected by an elevation in aminotransferases. Cholestatic injury occurs from blockage or damage to the biliary tree and is often reflected by elevations in bilirubin, gamma-glutamyl transferase and alkaline phosphatase. Agents with particular risk include ddI, d4T, AZT, all PIs (especially full dose ritonavir) and all NNRTIs. The prolonged use of ddI has been reported as an independent risk factor for liver fibrosis and non cirrhotic portal hypertension in adults.[27] The most prominent risk factors for hepatotoxicity on HAART are concomitant opportunistic infections and chronic viral hepatitis (hepatitis A, B, C or D, CMV and EBV), being less frequent in children than adults.[18,28] With the nucleosides reverse transcriptase inhibitors (NRTIs), the predominant mechanism appears related to mitochondrial DNA damage which also may lead to lactic acidosis and less frequently in children, to peripheral neuropathy, pancreatitis and myopathy.[29] The mechanism for PI hepatotoxicity is unknown. NNRTIs cause two distinct hepatic syndromes, more common with nevirapine: acute hypersensitivity reaction within 6 weeks after initiation of therapy, with frequent rash and eosinophilia; and a delayed variant that occurs after weeks of exposure, often without extrahepatic manifestations. Fatal liver damage has been reported in HIV negative adults receiving nevirapine postexposure prophylaxis, suggesting that normal or near-normal CD4 counts are required for fulminant hepatitis to occur. It is also more common in HIV infected adults initiating treatment with higher CD4 cell count.[30] It has seldom been reported in HIV infected children.[29] Efavirenz-related liver toxicity may have an independent mechanism and is usually mild.

The most commonly used markers to screen for hepatocellular injury are aspartate aminotransferase (AST) and alanine aminotransferase. Both of these markers are sensitive for injury but have poor specificity and prognostic value. Hepatic injury is often defined as increases in AST/ALT levels that are 3 to 5 times more than the upper limits of normal of the patient's baseline values before initiation of antiretrovirals. Many patients have mild increases in their AST/ALT levels within the first few months of antiretrovirals, which may occur with or without symptoms and return to normal levels thereafter. It is also common to have a rebound in aminotransferases shortly after programmed interruption of HAART in children.[32]

The PIs have also been associated with hyperbilirubinemia in adults and children. Atazanavir and indinavir cause unconjugated hyperbilirubinemia without increase in transaminase levels. About 40 percent of individuals receiving atazanavir develop a significant increase in their total bilirubin level, 5 percent of patients develop clinical jaundice, although none of them develop clinically significant hepatotoxicity. Jaundice is reversible if the drug is discontinued, but this may not be needed if the patient is asymptomatic. Nevertheless, a mild and subclinical jaundice may be very troublesome for some patients, particularly adolescents and often lead to discontinuation of atazanavir and switching to another antiretroviral. The increase in total bilirubin level observed with these PIs may be caused by a similar mechanism as Gilbert syndrome involving inhibition of UDP glucuronoyl transferase, an enzyme required for conjugation of bilirubin. Similarly, indinavir (no longer used) causes hyperbilirubinemia in 10 percent of patients, also without any other evidence of hepatotoxicity. Hyperbilirubinemia from the PIs are not associated with hepatotoxicity and should not be confused with posthepatic cholestasis.[26]

Hypersensitivity syndrome is a life-threatening condition that is caused by an immune reaction to either the parent drug or a metabolite. Hepatotoxicity may also be a component of a potentially fatal hypersensitivity reaction with nevirapine that may present as fever, rash (including Stevens-Johnson), eosinophilia, shock and renal failure. For nevirapine, 2 weeks of half-dosing decreases the chance of this complication. For these reactions, the drug should be discontinued and rechallenge can result in death. Close monitoring is strictly necessary in the first weeks since its initiation. Corticosteroids have failed to show any benefit in prophylaxis and therapy.[26,30] The syndrome of abacavir hypersensitivity occurs in 3-8 percent of Caucasians taking the medication and is strongly associated with the HLA-B5701 haplotype. It is currently recommended to screen for this haplotype prior to initiating abacavir.[31] The presence of the drug evokes an immune-mediated response that can affect the liver as well as other organs, such as the skin, lungs, kidney and heart. It most often

occurs within the first few days of therapy, but may occur as late as 8 weeks. The most common symptoms are fever, rash, nausea and vomiting. In abacavir hypersensitivity, 80 percent of patients have fever and 70 percent have rash. Patients may also exhibit myalgias, headache, diarrhea, pruritus, lymphadenopathy, mucocutaneous involvement, hypotension and respiratory symptoms such as cough, dyspnea, or pharyngitis. Hypersensitivity is usually associated with increased transaminase levels in addition to the presence of other laboratory abnormalities such as leukopenia, thrombocytopenia, increased serum creatinine level, increased creatine phosphokinase level and eosinophilia. It is critical to have a high suspicion for the presence of this syndrome and stop the drug immediately, since it may progress rapidly to multisystem organ failure. Although it may be difficult to distinguish hypersensitivity from infectious or other underlying disorders, it has been recommended that all antiretrovirals be held if the patient has 2 or more of the following symptoms: fever, rash, gastrointestinal symptoms, constitutional symptoms and respiratory symptoms. In patients with mild symptoms or less than 2 of these symptoms, patients may continue to take their medications with close observation. The vague nature of these symptoms may result in overdiagnosis of hypersensitivity, unnecessarily precluding the use of the suspected drug in the future. Cessation of the offending agent is currently the only effective treatment, with resolution of most symptoms within 48 to 72 hours. It is very important to be aware that several medications combine abacavir with other drugs under completely different names and patients may not appreciate this potential hazard of unintended rechallenge.[31]

Mitochondrial damage is believed to be a prominent cause of hepatic steatosis. The NRTIs can reduce the replication of mitochondrial DNA (mtDNA) in a manner similar to their effects on the HIV DNA replication. Oxidative phosphorylation is impaired, which leads to an accumulation of fatty acids and other precursors in the cell. Hepatic steatosis may have a relatively benign or even asymptomatic presentation and may also mimic other diseases. Patients may present with mild symptoms suggestive of hepatitis, such as abdominal pain, nausea and vomiting. Fatty liver also may occur in children receiving HAART with long-term use. Hepatic sequels for children receiving long-term HAART are unknown, but adult data raise concern for future liver dysfunction, even in children with low grade transaminase elevations or asymptomatic fatty liver, although hepatic steatosis rarely progresses to liver compromise. In addition, there is concern for adult life of the combined effects of several related metabolic and endocrine disorders, including glucose intolerance, metabolic syndrome and cardiovascular disease.[29]

One of the most severe complications recognized as a risk of antiretrovirals is the development of symptomatic hyperlactatemia with metabolic acidosis that may be fatal also in children and adolescents. Hyperlactatemia occurs when plasma lactate is above the normal limit without laboratory evidence of acidosis. Lactate increases are classified as mild (2–5 mmol/L), moderate (5–10 mmol/L) and severe (>10 mmol/L). Lactic acidosis is considered if the pH is less than 7.3 and bicarbonate below 20 mEq/L with any abnormal increase in serum lactate level. The diagnosis may be difficult initially. Patients may present with fatigue, general malaise, nausea, vomiting, abdominal pain, hepatotoxicity, tender hepatomegaly, peripheral edema and ascites. Severe cases may progress rapidly to cardiomyopathy, encephalopathy, peripheral neuropathy, pancreatitis, pancytopenia, fulminant hepatic failure and cardiopulmonary shock. It is important to have a high index of suspicion since the signs and symptoms are non-specific and lactic acidosis is associated with high mortality in adults and children.[29] In patients with no symptoms, a screening lactate is not indicated because it has poor positive predictive value. Because of the vague nature and poor correlation of symptoms to the degree of increase in lactate or acidosis, children on antiretrovirals who present any systemic complaints should be screened with a venous lactate, pH, bicarbonate level and a hepatic function work-up. Lactic acidosis may develop within months to years after the initiation of antiretroviral treatment (mainly the thymidine analogs). Factors that increase the risk for this adverse event include NRTI use greater than 6 months, pregnancy, female sex, lower CD4 count, stavudine and concurrent use of ribavirin for hepatitis C.[29]

Pancreatitis is a common adverse event attributable to antiretrovirals, but less frequent in children than adults. Advanced HIV disease alone is associated with an increased incidence of pancreatitis, but NRTI use is independently linked to this complication.[33] Risk factors identified for this complication include high-dose didanosine, CD4 count less than 200 cells/mm^3, older age, increased baseline amylase and female gender. Pancreatitis occurs most often 2 to 5 months after the initiation of antiretroviral treatment, with complaints similar to patients with non-antiretroviral causes of pancreatitis, including nausea, abdominal pain, vomiting and fever and a high mortality rate. The mechanism of pancreatic toxicity may be related to the mitochondrial toxicity of NRTIs, as discussed earlier for lactic acidosis and hepatic steatosis. PIs often induce hyperlipidemia, a known cause of pancreatitis. Patients who have clinical symptoms consistent with pancreatitis while on antiretroviral treatment should have serum lipase concentrations measured. Increase in pancreatic enzymes 2 to 3 times more than normal with clinical symptoms



Fig. 2.10.1: Extensive lesions of candida in the oral mucosa and anterior pillars of the pharynx



Fig. 2.10.2: Typical appearance of oral hairy leukoplakia on the lateral border of the tongue

confirms this diagnosis. There is no evidence to support the screening of pancreatic enzymes in patients who are asymptomatic. Patients who develop pancreatitis while on antiretrovirals are treated by discontinuing the drug and providing supportive care including bowel rest, analgesics, intravenous fluid therapy and parental nutrition if needed. In addition, controlling hyperlipidemia in patients on PIs may prevent as well as treat pancreatitis.[33]

Upper GI Disease

The upper GI tract is a very common site for complications in HIV infected children, closely linked to the degree of immunosuppresion. Since the introduction of HAART, a decline in oral manifestations has been observed. The inflammation that accompanies the different array of conditions involving the upper GI tract may be painful and adversely affect the amount of food a child consumes, further compromising the poor nutrition present in advances stages of immunodeficiency. The spectrum of the clinical lesions in the oral cavity in HIV infected children differs considerably from that of adults.[34] Oral candidiasis (thrush) is the most common fungal infection in HIV infected children[18] (Fig. 2.10.1). Without antiretroviral treatment, most children have thrush, being frequently the first manifestation of HIV infection. In addition, recurrent thrush is the norm in HIV infected children and should alert about an unrecognized underlying HIV diagnosis. Furthermore, in children on HAART, oral candidiasis is usually the first clinical sign of therapeutic failure subsequent to immunological deterioration occurring months after virological failure and should prompt a change of therapy. In older children, lesions of oral candidiasis usually present when the CD4 count is less than 200/mm^3. The lesions may present with mild oral pain and a burning sensation while eating. Older children may also refer ageusia and odynophagia. The creamy white lesions are located on the tongue surface and on the buccal mucosa. Occasionally, they may be asymptomatic. Diagnosis is reached by clinical examination and demonstration of yeast forms and pseudohyphae on potassium hydroxide (KOH) preparation. Culture of the scrapping will be useful in identifying the species of the yeast responsible for the infection, *C. albicans* by far being the most common. Lesions usually respond to topical miconazole or nystatin, although occasionally they require oral fluconazole or itraconazole.[18]

Candida lesions in the tongue may mimic oral hairy leukoplakia (OHL) that is a benign manifestation of the EBV and HIV coinfection, less common in children than in adults. OHL most commonly appears in the lateral borders of the tongue as flat, white, vertically corrugated (resembling hair) lesions (Fig. 2.10.2). Although usually subclinical and asymptomatic, mild symptoms may be the result of *Candida* coinfection, what frequently occurs. OHL has been reported as a predictor of disease progression in children in the preHAART era.[35] It is closely linked with immune status, as demonstrated by the fact that the lesions regress as immune status improves with HAART.[36]

Painful oral lesions are caused more frequently by herpes simplex virus (HSV). They show common vesicles that breakdown to form ulcers and have a tendency to be severe and remain for a longer duration in patients with advanced HIV as compared with the normal population.[18] In children, HSV may present with recurrent episodes of gingivostomatitis like in primary infection and are associated with a high morbidity and frequent admissions to hospital. Currently, viral cultures, HSV/DNA

polymerase chain reactions and HSV serological antigen studies are strongly recommended to ascertain the diagnosis in HIV positive patients. Lesions usually respond to oral acyclovir and in older children also famciclovir or valacyclovir, prescribed over a period of 5-10 days. Intravenous acyclovir is however recommended for severe mucocutaneous herpes infection. Acyclovir-resistant strains, suspected by failure of response within 7-10 days, should be managed with foscarnet, which is the drug of choice.[28]

Another common lesion in advanced disease in children is idiopathic aphthous ulcer that may be minor (<1 cm) or major (>1 cm), usually very painful and compromise oral intake. It may respond to topical steroids and analgesics, but in refractory cases may require oral steroids or thalidomide. After the introduction of HAART they are very unusual.[34]

Dysphagia should lead to the suspicion of esophageal involvement in children with advanced stages of immunosuppression (<100 cells). The differential diagnosis of children with dysphagia is broad. *Candida* esophagitis is the most common cause. The diagnosis of *Candida* esophagitis in children is usually done on clinical grounds without upper endoscopy. If the patient does not respond in the first few days to an empiric oral azole treatment, endoscopy is usually indicated because other infections may also produce esophageal lesions, like CMV or HSV, that may be alone or in association, or idiopathic esophageal ulceration. CMV and *Candida* coexist in up to 20 percent of adult patients with esophagitis.[28] Occasionally, patients with advanced disease may have esophageal aphthous ulcers that may present without oral lesions. Other AIDS-related disorders causing dysphagia described in adults are tumors that are very unusual in children. In the era of HAART, many of these previously common HIV related disorders have essentially vanished. Nevertheless, they may occur in patients failing HAART or who are not compliant.[37]

When approaching any patient with upper GI complaints, assessment of the stage of immunodeficiency is necessary as reflected by the CD4 cell count and in children younger than 6 years of age, also the percentage that is a stronger predictor of the risk of progression and better estimates the degree of immunodeficiency (Fig. 2.10.3). *Candida* and HSV esophagitis are predominantly documented in patients with CD4 counts less than 200/mm^3 whereas CMV is almost exclusively seen with CD4 counts below 100/mm^3. Given the preponderance of candidal infection and the classic examination findings, empirical treatment with either oral fluconazole or itraconazole is indicated. Both have a superior efficacy over ketoconazole.[28] Although studied in HIV infected adults, no data exist on the use of echinocandins in the treatment of HIV infected children. A lack of response to empiric azole therapy should prompt an upper GI endoscopy and histologic examination. In a recent study in South African children, endoscopy findings disclose a broad spectrum of infections and influenced clinical management in 80 percent of children affected of persistent upper gastrointestinal symptoms. Pathogens identified included CMV, *Candida*, *Helicobacter pylori* and *Cryptosporidium*.[38] *Histoplasma capsulatum* may also present as oropharyngeal ulcerations.[28] Achieving an etiologic diagnosis is important because of the complex specific treatment required. Herpes esophagitis usually responds to acyclovir. Foscarnet is active against acyclovir-resistant herpes simplex. Established infections with CMV usually respond to a course of ganciclovir or foscarnet followed by oral valganciclovir for 21-28 days or until resolution.[28]

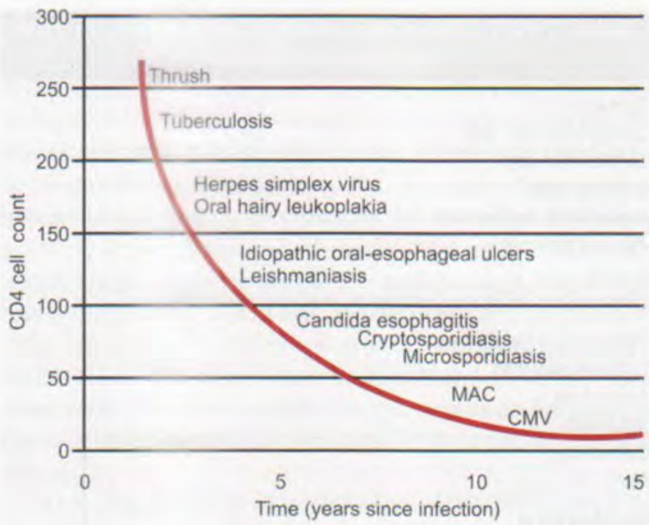


Fig. 2.10.3: Natural history of untreated HIV infection and relationship of specific OI to CD4 count

Diarrhea

Diarrhea is the most common GI symptom in patients with HIV infection. Prevalence ranges from 0.9 to 14 percent.[19] Infants and children with HIV infection have more frequent and more severe diarrhea than children without HIV, leading commonly to chronic diarrhea, mainly in advanced stages of the disease. A wide variety of bacterial, viral, mycobacterial and protozoal pathogens are responsible for diarrhea in HIV infected children patients. The differential diagnosis is broad (Table 2.10.2). In the preHAART era, an etiologic diagnosis could be achieved in 50-75 percent of patients after an extensive investigation. GI opportunistic infections are commonly encountered at various stages of HIV disease. Virtually all OI occur when the CD4 cell count is less than 200/mm^3 and subsequently responds to the immune reconstitution facilitated by HAART.

Table 2.10.2: Infectious etiology of diarrhea in HIV infected children

Bacteria
Campylobacter spp.
Salmonella spp.
Shigella spp.
Aeromonas hydrophila
Vibrio cholerae
E. coli
Clostridium difficile (antibiotic induced diarrhea)
Virus
Cytomegalovirus
Astrovirus
Rotavirus
Calicivirus
HIV?
Mycobacteria
Mycobacterium avium complex (MAC)
Mycobacterium tuberculosis
Parasites
Cryptosporidium spp.
Microsporidia spp.
Isospora spp.
Cyclospora
Blastocystis hominis
Entamoeba histolytica
Giardia lamblia

Although the opportunistic causes of diarrhea have markedly fallen after the introduction of HAART, the proportion of patients diagnosed with non-infectious causes of diarrhea have increased, partly due to antiretroviral therapy, but also due to the fact that as patients are now living longer, they have exposure to other pathogens that may result in disease and also to antibiotic-induced diarrhea from *Clostridium difficile*.[19]

There are two common syndromes of infectious diarrhea. Enteritis is caused by pathogens that affect the small bowel in which watery diarrhea predominates and ileocolitis in which a dysentery-like illness predominates characterized by the presence of fever, abdominal pain, cramping and frequent stools with mucus and blood. Enteritis can be caused by common pathogens in childhood, including rotavirus, adenovirus, enterotoxigenic *E. coli* and *Giardia lamblia*. Causative agents of enterocolitis include *Salmonella, Campylobacter, Shigella and Clostridium difficile*. Opportunistic pathogens such as CMV, MAC, *Cryptosporidium, Microsporidium* and *Isospora* are frequently implicated in advanced stages of the disease. The incidence of bacterial gastroenteritis is higher in infants, in whom bacteremia are common.[18,39] In addition, the risk of dissemination increases in parallel with the degree of immunosuppression. The most frequent bacterial pathogen are *Salmonella* spp. *Campylobacter* spp. that may be difficult to eradicate in advanced stages of immunosuppression. These pathogens may present as recurrent, severe bloodstream infections with mild GI symptoms.[18,39,40]

Viruses are also very frequent causes of diarrhea in HIV infected children. Common enteric viral infections in childhood like rotavirus or adenovirus may result in protracted diarrhea and the shedding in stools prolonged. Although, some studies have shown that HIV seropositive children with diarrhea were more likely than their counterparts without diarrhea to have rotaviruses and that rotavirus is an important viral etiological agent causing diarrhea in HIV seropositive children in developing countries, a recent review suggest that rotavirus does not cause more frequent or more severe disease in children with HIV infection. Nevertheless, there are data from a South African cohort that indicate that the burden of acute gastroenteritis is two-fold greater among HIV infected and this could also translate into an increased burden of hospitalization for rotavirus disease.[41]

Parasites are frequent causes of chronic diarrhea and malnutrition in HIV infected children in developing countries. In some areas, the prevalence of intestinal parasitic infection in immunocompromised children with persistent and/or recurrent diarrhea is high. *Cryptosporidium* is the genus most commonly encountered, followed by *Microsporidium* spp. Other parasites frequent in advanced immunocompromised HIV infected children in developing countries are *Cyclospora cayetanensis* and *Isospora belli*. In some areas of Asia, *Blastocystis hominis* infection has been reported as the most common parasite in children with chronic diarrhea.[42]

Although the incidence of cryptosporidiosis and microsporidiosis infection is higher in developing countries, they are present worldwide. *Cryptosporidium* diarrhea is a common OI in advanced HIV disease in children. Although microsporidiosis has been reported more frequently in adults, it is also an important cause of chronic diarrhea in severely immunocompromised HIV infected children.[43] Although many microsporidia have been reported as pathogens in humans, *Enterocytozoon bieneusi* (mainly genotype D) and *Encephalitozoon intestinalis* are the most common microsporidia that cause infection among HIV infected patients. *Enterocytozoon bieneusi* is an important cause of persistent diarrhea, intestinal malabsorption and wasting in HIV positive adults and children. Mucosal damage associated with microsporidiosis is more extensive than that related to other opportunistic intestinal infections and leads to substantial malabsorption of carbohydrates, fat and essential nutrients. The most common manifestation of microsporidiosis is watery acute and chronic diarrhea,

but has also been rarely involved in hepatitis, peritonitis, keratoconjunctivitis, myositis, cholangitis, respiratory disease, sinusitis, encephalitis and disseminated disease.[18,42] Clinical history or physical examination does not allow differentiation of cryptosporidial or microsporidial disease from those caused by other pathogens. Frequent, usually nonbloody, persistent watery diarrhea is the most common manifestation of both cryptosporidial and microsporidial infection, with abdominal cramps, fatigue, vomiting, anorexia, weight loss and poor weight gain. Fever, usually low-grade and vomiting are relatively common in children, mimicking viral gastroenteritis. In severe cases of chronic diarrhea, it may be severe leading to malnutrition, failure to thrive and substantial intestinal fluid losses, resulting in severe dehydration and even death. *Cryptosporidium* spp. can migrate into the bile duct and result in inflammation of the biliary epithelium, causing acalculous cholecystitis and sclerosing cholangitis[44] (Fig. 2.10.4). Common symptoms and signs include fever, right upper abdominal pain and elevated alkaline phosphatase. Both pancreatitis and disseminated disease are rare in children.

Colitis is the most common GI manifestation caused by CMV. Abdominal pain and hematochezia frequently occur with CMV colitis. In advance HIV disease, colonic ulcerations may lead to perforation and severe hemorrhage. Other complications of CMV include ascending cholangitis and pancreatitis. Since sigmoidoscopy in CMV colitis is nonspecific, demonstrating diffuse erythema, submucosal hemorrhage and diffuse mucosal ulcerations, histologic examination is usually required for diagnosis.[45] Multiple biopsies increase the diagnostic yield.[19]

Chronic diarrhea is also a common manifestation of *Mycobacterium avium complex* (MAC) infection in severely immunocompromised HIV infected children. Diarrhea is usually associated with other signs and symptoms of disseminated MAC infection that are nonspecific, including persistent or recurrent fever, weight loss or failure to gain weight, sweats, fatigue and persistent or recurrent abdominal pain. Lymphadenopathy, hepatomegaly and splenomegaly are common as well as anemia, leukopenia and thrombocytopenia. Although serum chemistries are usually normal, some children may have elevated alkaline phosphatase or lactate dehydrogenase.[46] Although a less common pathogen involved in GI symptoms in children, *Mycobacterium tuberculosis* can also involve the gut and is an important cause of disease in HIV infected patients in the developing world.[19]

The diagnostic evaluation of an HIV infected child presenting with diarrhea should be guided by the duration of the diarrhea, the clinical syndrome as well as the HIV disease status. Many episodes of acute enteritis do not require diagnostic evaluation. Nevertheless, if GI symptoms are severe or persistent, admission to hospital should be considered along with a number of investigations, that include antigen detection for common viruses, stool culture for bacterial pathogens and blood culture as well as toxin detection for *Clostridiun difficile* if there is a history of recent antibiotic use. Routine stool culture has a variable yield, depending on the epidemiological setting and CD4 cell count. The diagnosis of OI in HIV infected is usually straightforward. However, subtle presentations require that the physicians should have a high index of suspicion when given the setting of HIV infection. Further investigations should include a 3 consecutive days processing for parasites and a modified Kinyoun acid-fast staining of stools for detection of oocysts of *Cryptosporidium* (Fig. 2.10.5), *Isospora* and *Cyclospora*,



Fig. 2.10.4: Endoscopic retrograde cholangiopancreatography (ERCP) showing dilation of the common bile duct and intrahepatic ducts due to common bile duct stenosis caused by cryptosporidium

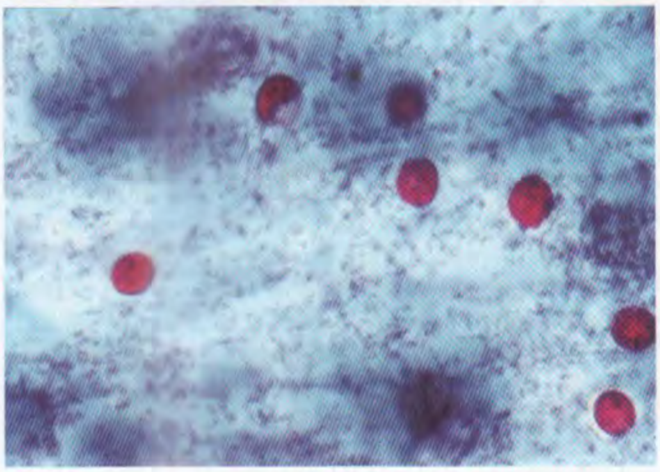


Fig. 2.10.5: Oocysts of cryptosporidium in stools visualized with a modified Kinyoun acid-fast staining

or a modified trichrome stain for *Microsporidium* spores. Occasionally duodenal aspirates are required for their detection. Repeated blood cultures with radiometric methods are sensitive for the detection of MAC. Colonoscopy should be considered in children with dysentery who do not harbor an identified pathogen. In chronic diarrhea lasting more than 2 months and negative stool examination and negative evaluation, endoscopic biopsy is also indicated. Biopsies are obtained for evaluation of bowel histology and detection of common opportunistic pathogens such as CMV, MAC, cryptosporidia and microsporidia.[19,28] Endoscopic examination with biopsy may establish the diagnosis in 65-82 percent of patients with negative stools tests.[19] Severe diarrhea where no pathogen can be identified despite extensive investigation with endoscopy and biopsy has been ascribed to HIV enteropathy. This enteropathy is extremely uncommon in the era of HAART.

The management of the HIV infected child with diarrhea must include close attention to nutritional support. Empiric antibiotic treatment should be considered for the child with dysentery and also in advanced stages of the disease. Other therapeutic interventions should by guided by the results of diagnostic studies. Effective antimicrobial therapies are still lacking for some of the opportunistic infections resulting in diarrhea in HIV infected children, including *E. bieneusi*. Advances have been made in some antiparasitic drugs such as nitazoxanide for criptosporidiosis, although the existing evidence is limited primarily to non-immunocompromised children.[47] Consideration should be given to start early antiretroviral therapy since restoration of immune function is required to recover from most opportunistic enteric pathogens and HAART remains a cornerstone of treatment of OI, although caution must be given to possible drug-drug interactions, adverse effects and the possible overlapping signs and symptoms of IRIS.

Hepatobiliary Disease

Diseases of the hepatobiliary system are a major problem in patients with HIV infection. An estimated one-third of deaths in HIV patients are directly or indirectly related to liver disease. Liver diseases in HIV infected persons can occur due to hepatitis B virus (HBV) and hepatitis C virus (HCV) co-infections, other hepatotropic viruses, OIs, or due to the effects of antiretroviral therapy. In addition, sepsis and malnutrition may also contribute to liver damage. In the preHAART era, most children had hepatobiliary manifestation of the disease in advanced stages. In severely immunocompromised children, OIs frequently are associated with hepatobiliary involvement, including disseminated MAC infection, extrapulmonary tuberculosis, CMV, disseminated cryptococcosis and histoplasmosis. Liver involvement associated with *Pneumocystis jirovecii* infection occurs in up to one-third of patients and may be identified in liver biopsy. Cryptosporidiosis and microsporidiosis may be associated with acalculous cholecystitis in patients with advanced AIDS. These patients usually present with right upper quadrant pain and abnormal liver profile. Biliary involvement is the most common extraintestinal manifestation of the cryptosporidiosis in HIV infected patients. Clinical features are right upper quadrant pain, nausea, vomiting and fever, usually low-grade, accompanied by elevated alkaline phosphatase levels.

Hepatitis

Hepatomegaly and abnormal liver function tests are often seen in children without antiretroviral treatment. A mild increase in aminotransferase is frequent, usually asymptomatic with normal bilirubin and alkaline phospatase. A histologic picture similar to chronic persistent hepatitis with lymphoplasmocytic infiltration has been described in children.[48]

As is true for the GI tract, infectious agents represent a significant source of hepatobiliary disorders in HIV infected children. The liver is often not the primary site of involvement, but part of disseminated disease. Hepatitis may be caused by a variety of micro-organisms, among which the hepatotropic viruses predominate. The most important ones are HBV and HCV, but CMV, EBV, hepatitis A (HAV), hepatitis D and hepatitis E may also cause hepatitis.[18]

The prevalence of coinfections with HBV and HCV in children perinatally infected with HIV varies geographically and have been scarcely documented. Overall, the prevalence is lower than in HIV infected adults, but higher than in children without HIV infection,[49-52] since they share the same transmission routes than HIV, including mother to child transmission, that is the most common mode of transmission of these viruses worldwide in HIV infected children. HBV acquired perinatally results in chronic infection in most children. Nevertheless, an important mode of acquisition of HBV is through sexual contact and through exposure to HBV infected household contacts. In a study of HIV infected youth at 45 centers in the USA, 19 percent of patients were determined to have been coinfected with HBV, either current or resolved.[49]

These coinfections have been associated in adults with reduced survival, increased risk of progression to liver disease, including cirrhosis and hepatocarcinoma and increased risk of hepatotoxicity associated with

antiretroviral therapy.[53] Until the advent of HAART, the hepatotropic viruses played a little role in the long-term outcome of HIV infected patients, because the clinical course was dominated by the opportunistic diseases associated with HIV. However, after the introduction of HAART, as the life expectancy has increased, end-stage liver disease has become a major problem in adults infected with HIV and an issue of major concern in those children perinatally infected who have either HBV or HCV. The higher prevalence of these coinfections observed in many parts of the world should prompt for screening for hepatotropic viruses in all children infected with HIV.[50,51] In addition, the antiviral effect against HBV of some antiretroviral drugs commonly used in children should also be considered when choosing a specific antiretroviral regimen in a setting with a high prevalence of HBV.[18]

Few data exist concerning HIV/HCV co-infected pediatric population. Since blood products are tested for HCV, vertical transmission has become the main transmission mode of HCV in children. Maternal HIV/HCV coinfection is the major source of HIV/HCV coinfection in childhood, although there are also groups of children with parenterally-acquired coinfection. Prevalence of HIV/HCV coinfection in pregnant women in Europe varies considerably and is estimated to range from less than 5 to 50 percent. Maternal HIV coinfection increases the risk of perinatal HCV transmission, with perinatal transmission rates of 6-23 percent reported for infants born to women coinfected with HCV and HIV, in contrast with less than 10 percent for those born to women infected with HIV alone.[18]

The predominat genotype causing HCV disease in children in the United States and Europe is genotype 1.[54] Genotype 3 is associated with higher inflammation but better response to treatment, similarly to genotype 2. As patients with HCV genotypes 2 and 3 are more likely than those with genotype 1 or 4 to achieve sustained virologic response to anti-HCV therapy, the results from a liver biopsy may be less likely to affect decisions about the need for treatment in patients with genotypes 2 or 3.[18] Therefore biopsy is not usually performed to treat patients coinfected with genotype 2 and 3. Currently, liver transient elastography (Fibroscan) is increasingly being used as a rapid, non-invasive ultrasound technique to measure the liver stiffness although it does not provide information about the degree of necrosis and inflammation. It has shown good correlation with liver biopsies both in non-HIV infected and HIV infected adults which is an important advance in the management of coinfected patients.[55,56] Although it has not been validated in children, it may be a valuable tool to monitor the progression of liver disease and guiding therapeutic decisions in clinical practice in coinfected children, avoiding the need of a biopsy, especially in earlier stages of fibrosis.

The natural history of HCV coinfection is altered by coinfection with HIV. In coinfected patients, HCV viral load is much higher than in HIV negative patients. HCV-specific CD8 T cell activity is reduced and there is more rapid progression to liver fibrosis. In addition, coinfection of HBV or HCV may compromise antiretroviral therapy.[53] There are very few studies about the degree or fibrosis and its progression in HCV/HIV coinfected children. There is very scarce information on the histopathology of hepatitis C in coinfected children and adolescents. In a French study, 7 coinfected adolescents were biopsied and in all there was mild fibrosis.[57] Nevertheless, a small subset of children may develop more severe liver disease. In a study of 60 children with perinatally acquired or transfusion acquired HCV infection who were infected for a mean duration of 13 years, 12 percent had significant fibrosis on liver biopsy.[58] Even with mild histological necroinflammatory activity in general, the stage of fibrosis in children can be severe in spite of relatively short duration of infection. It is generally assumed that the fibrosis progression is slow in the first decade after birth and probably slow in most children thereafter, but the progression to liver fibrosis is accelerated in HIV coinfected adolescents perinatally infected as compared with HCV monoinfected patients.[58,59] Furthermore, occult HCV infection may be more frequent in HIV infected children perinatally infected with HCV than in patients infected through other routes of infection.[59] Occult HCV infection as defined by detectable HCV RNA in serum in the absence of HCV antibodies has been observed in HIV infected adults in advanced stages of immunosuppression. By contrast in HIV infected children and adolescents perinatally-infected, occult infection may occur with high CD4 cells,[59] suggesting that HCV acquired perinatally may not lead to an adequate specific antibody response despite high degree of viral replication. Therefore in children at risk of acquiring HCV infection, such as those children born to coinfected mothers, plasma HCV RNA should be done even if HCV antibodies are negative, either in older children when first tested, or in infants when antibodies become negative in the first months postnatally.[59]

The current recommended regimen for treatment of coinfected adults, pegylated interferon alpha 2b or 2a plus ribavirin, is not approved for it's use in children and there are no specific guidelines or currently HCV therapy recommendations for HIV/HCV coinfected pediatric population. Nevertheless, recent trials of pegylated interferon plus ribavirin on HCV mono-infected children have shown good responses and acceptable tolerance.[60] There is no data available about HCV treatment and outcome of HCV/HIV coinfected children. In addition,

there is no appropriate dosing information for use of pegylated interferon alpha or ribavirin to treat HCV in children. To date, no studies have been carried out specifically investigating anti-HCV therapeutic management of children coinfected with HIV and HCV.[18] Treatment decisions in these children thus tend to be based on adult data or extrapolate recommendations for the management of HCV-monoinfected children. A recent European survey found that therapeutic management of HIV/HCV coinfected children varied widely in the absence of specific guidelines and revealed a very limited experience of treating coinfected children for HIV and HCV concurrently.[61]

HBV infection leads to chronic hepatitis in more than 90 percent of vertical infections and about 10 percent if the infection occurs in older children and adults. In coinfected individuals, the liver-related mortality rate was highest with lower nadir CD4 cell counts. Progression to liver cirrhosis and hepatocellular carcinoma is faster than in HIV negative patients. Furthermore, the median HBV DNA is higher in HIV coinfection. After initiation of HAART, liver function may worsen due to IRIS causing an immune response to HBV in the liver and subsequently a flare of hepatitis. Unlike HCV, HBV has no detrimental effect on the course of HIV infection. However, hepatotoxicity associated with antiretroviral treatment is about 3 times more frequent in chronic hepatitis B coinfection than in HIV monoinfection.[18]

Similarly to HCV, there is very little experience on the treatment of HBV in coinfected children and adolescents. Indications for treatment of chronic HBV infection in HIV coinfected children are the same as in HBV infected children without HIV infection. Antiviral treatment should be considered in children with chronic HBV infection and a duration of necroinflammatory liver disease greater than 6 months.[18] In order to prevent flares of the disease and the development of resistance, dual anti-HCV drugs should be used in the setting of HAART whenever treatment of HCV is indicated in a coinfected child. Due to the fact that there are few drugs available for children with activity against HBV, tenofovir should be considered in children and adolescents in combination with either lamivudine and emtricitabine.[21,62] Immunization against HBV and HAV is strongly recommended in all HIV infected children, especially those with liver disease. The antibody response elicited by these vaccines are more likely to be higher and protective when HAART has been initiated and there is an appropriate CD4 cell response documented.

Pancreatitis

The incidence of pancreatitis has been estimated to be between 4 percent and 22 percent in adult patients. Although it is less frequent in children, in the preHAART era, one study of children and adolescents in Boston, found that 17 percent of all patients with AIDS has pancreatitis.[63] It presents with abdominal pain in patients with advanced HIV disease, occurring because of diverse reasons. Apart from drugs, infections are responsible for acute pancreatitis, including CMV, *M. tuberculosis*, MAC, *Cryptococcus neoformans*, *P. jirovecii*, *Toxoplasma gondii* and *Leishmania* spp. Besides the potential pancreatic toxicity of some antiretrovirals, several other antimicrobials used for OIs may also cause pancreatitis including trimethoprim-sulfamethoxazole, pentamidine and some antimycobacterial drugs. In assessing children, there should be a high index of suspicion in a setting of HIV disease plus abdominal pain and elevated amylase and lipase. Lipase levels are more reliable indicators of pancreatitis than amylase levels. Amylase increase may also be of salivary origin. Abdominal ultrasound examination will generally reveal features typical of pancreatitis, including a swollen, edematous pancreas, occasionally with ascites. The biliary tract should be evaluated because pancreatitis may be secondary to a primary biliary obstruction. The course of the disease may be severe with high mortality. Exacerbations of the disease may occur for prolonged periods. The benefit of HAART along with the dramatic reduction of OIs, has led to a marked decrease in the incidence of pancreatitis in children. Amylase or lipase assessment is not usually monitored in the absence of signs or symptoms of pancreatitis during the routine follow up of HIV infected children.

With the advent of HAART, children are living longer and with a better quality of life. In many parts of the world, most perinatally infected children are entering adolescence and many transferred to adult units. Nevertheless there is concern for the long-term complications of HAART and the future impact of HIV and related coinfections in different organ systems, including non-HIV related disorders and neoplasia. It is of utmost importance to ensure a long-term follow up of HIV infected children to elucidate the natural course of perinatal infection in an era in which the complete and maintained suppression of viral replication is a reality but also a challenge.

Key Messages

- The widespread use of HAART has altered the management of gastrointestinal and liver involvement in children
- Gastrointestinal and liver involvement in HIV infected children is currently more frequently due to adverse effects of antiretroviral drugs than to opportunistic infections or AIDS-related diseases.

☛ Hepatitis B and C coinfections are of major concern worldwide. Better knowledge on the strategies for diagnosis and treatment is urgently needed in children.

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2.11

Growth/Development/Puberty in HIV Infected Children and Disorders of the Same

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Introduction

Growth and puberty represent two critical periods of life, during which many physical changes occur allowing children and adolescents to transit from childhood to maturity. Both of these times are affected by a number of factors, and especially genetic and environmental effects play a pivotal role. As a matter of fact, in many childhood chronic illnesses such as diabetes, cardiac diseases, renal failure and other long-term disorders, impaired growth and alterations in pubertal timing have been described.[1]

Human Immunodeficiency Virus (HIV) is a viral infection that progressively causes chronic multisystem alterations. In particular, metabolism and endocrine function are involved and growth dysregulation is common in children with HIV. Growth failure in vertically HIV infected infants is one of the most sensitive marker of infection or disease progression,[2] contributing to morbidity and mortality with as much as a fivefold increase in the risk of early death.[3]

Pediatric HIV infection is associated with linear and ponderal growth retardation. In addition, differing trajectories of infant and child growth pattern have been associated with different patterns of disease and mortality during adulthood.

Delayed sexual maturation is a further common clinical manifestation in girls and boys living with HIV. In the past, very little was known regarding pubertal development in children with perinatal HIV infection, as just few subjects reached pubertal age. Currently, the effectiveness of Anti-Retroviral Therapies (ART) have modified perinatal HIV infection into a chronic manageable illness, and a significantly growing number of infected children survive until adolescence and well beyond.[4] Delayed puberty in children with perinatal HIV infection has been correlated with the severity of the disease,[5] and part of the linear growth failure could be attributed to delayed sexual maturation. A better understanding of the mechanisms leading to the delay in puberty in HIV infected population might lead to adequate treatments and strategies saving psychological distress to these young people. In fact, a really delicate issue regards management of adolescents living with HIV because of social dysfunction and loss of self-esteem. Consequently, this young population requires effective interventions and care planning in order to ensure a good quality of life and adequate psychological support.

The mechanisms responsible for metabolic and endocrine dysfunctions in pediatric population living with HIV are not completely known. The causes of the HIV related growth and puberty dysregulation are complex and include HIV itself, immunologic dysfunctions, chronic and recurrent infections, neuroendocrine abnormalities, and nutritional deficiencies.[6,7] Moreover, despite ART representing the standard for treating HIV infection, some evidences documented that these therapies have several side effects, especially adverse metabolic effects.[8,9]

Timely diagnosis and appropriate treatment of these unfavourable conditions may lead to improvement or even normalization of growth and puberty in children living with HIV infection.

Epidemiology

Pediatric HIV is a leading cause of morbidity and mortality. In 2005, an estimated 2.3 million children were living with HIV worldwide; 530,000 became newly infected and 380,000 died. Out of the total HIV infected children worldwide, 63 percent are in Sub-Saharan Africa,[10] where it has been reported that over 90 percent of the infected children may have acquired the infection through mother-to-child transmission.[11] According to UNAIDS [Joint United Nations program on HIV/Acquired Immune Deficiency Syndrome (AIDS)] epidemiological analyses, about 1600 infants are daily born with HIV infection worldwide.[10] However, the rates of maternal-to-child transmission of HIV vary by geographical location. In industrialised countries, pediatric HIV

infection has largely been controlled. In these settings, HIV rates are less than 2 percent. On the contrary, in developing countries the real HIV impact is extremely different and HIV infection is still spreading. In Africa, high rates of maternal HIV infection and high birth rates as well as inadequate access to available interventions and prolonged breastfeeding increase the burden of pediatric HIV disease. In India the current seroprevalence is 0.36 percent, with an estimated 100,000 infected women giving birth to about 30,000 infected infants every year, adding to the large pool of Indian children living with HIV.[12]

However, after pediatric ART exposure, survival of children perinatally infected with HIV highly raised. In fact, during the pre-ART era, not more than 10 percent of infected children survived beyond 3 years after serological diagnosis. In contrast, mortality rate has significantly reduced by 70 percent.[4] In India, in 2005 the National AIDS Control Organization has increased diagnostic monitoring and access to ART, and many children have started a specific anti-HIV therapy living on into adolescence.[13] To date, however, adolescents are at particular risk to contract HIV infection because of high-risk behaviours and missed preventive measures. As a matter of fact, in India, it has been reported a large number of teens and young adults who acquired HIV infection are between the ages of 15 and 24 years.[14]

Children living with HIV continue to experience multisystem HIV related alterations, especially in resource-limited settings. Growth faltering is a major complication in children and adolescents living with HIV, with a really large proportion of infected children experiencing abnormal growth patterns. The worldwide rate of growth disorders is variable. Studies from Europe estimated a failure-to-thrive prevalence of around 50 percent in HIV infected children surviving to age of 5 years and treated with ART of modest efficacy.[15] In developing countries the rate of growth disorders seems to be worse. In fact, in a study performed in Congo, growth retardation was reported in more than 60 percent of HIV infected children surviving to age of 20 months.[16] Several studies in Uganda have described impaired growth pattern among children up to 5-years-old, with impaired linear growth occurring in 25 percent of children under the age of 2 years,[17] and in 50 percent of children up to the age of 5 years.[18] In South India, recent retrospective data from 248 HIV infected children aged between 1 and 12 years reported a high prevalence of growth failure, with underweight and stunted proportions of 55 and 46 percent respectively.[13] Furthermore, growth retardation was highly reported also in non-HIV infected children born from infected mothers.

However, also many comorbidities such as nutritional deficiencies and hemoglobin defects have a negative impact on linear and ponderal growth retardation in HIV affected children. In developing as well as in developed countries anemia occurs in 50-90 percent of HIV infected children.[19] Unfortunately, anemia not only is extremely common in HIV infected children, but represents also one of the most sensitive predictor of disease progression, contributing to morbidity and mortality. Furthermore, also nutrition deficiencies are likely to impact on the course of HIV infection, especially in untreated HIV infected children. Studies from India have reported a wide prevalence of malnutrition, ranging between 17-62 percent of children living with HIV.[20]

HIV infection has also been associated with delay in the onset of pubertal development.[21] Perinatally HIV infected children often experience delayed puberty when compared to their peers. These endocrine dysfunctions determine psychological distress as well as worsen adolescents' quality of living. The underlying mechanisms are not completely known, although it seems to be determined by endocrine dysfunctions and environmental factors.

Physiology of Human Growth and Development

Human growth represents a biological control system subject to genetic and environmental influences from conception to maturity.[22] In particular, growth is a complex process which require an harmonized action among several hormones.

The role of growth hormone (GH) in determining birth size and early postnatal growth is imperative. GH is synthesized and secreted from the somatotroph cells within the lateral wings of the anterior pituitary gland with a pulsatile pattern. Once secreted, GH binds to the target cells' surface via a specific GH receptor. The most widely known promoting effect of GH is to stimulate insulin-like growth factor-1 (IGF-1) secretion, a polypeptide protein hormone. The liver represents the principal site of IGF-1 production, although this hormone is generated also within other target tissues. This hormone circulates bound to an insulin-like growth factor binding protein (IGFBP), primarily IGFBP-3. IGF-1 has growth-stimulating effects on a wide variety of tissues. In particular, this hormone has stimulatory effects on osteoblast and chondrocyte activity promoting bone growth and consequently body growth. Furthermore, IGF-I also appears to play a pivotal role in muscle growth, stimulating differentiation and proliferation of myoblasts, amino acid uptake and protein synthesis. GH has important metabolic effects, stimulating protein anabolism in many tissues and enhancing fat utilization by stimulating triglyceride breakdown and oxidation in adipocytes. Finally, GH suppresses insulin-stimulated whole-body glucose uptake and enhances glucose

synthesis in the liver. The strong secretory GH pulses generally occur after the onset of deep sleep. Its physiological secretion is under control of growth hormone releasing hormone (GHRH), a hypothalamic peptide stimulating synthesis and secretion of GH, and ghrelin, a peptide hormone secreted from the stomach stimulating GH production. In addition, GH is also under control of hypothalamic somatostatin which inhibits GH release in response to GHRH and to other stimulatory factors such as low blood glucose levels. Additionally, IGF-I inhibits GH synthesis and secretion in a negative feedback regulatory manner, by reducing amplitude of GH pulses and stimulating somatostatin release in presence of high blood levels. Finally, also other factors such as nutrition, exercise and stress modulate GH production.

Growth process has been defined as physical growth in terms of weight, height, head circumference and other body changes that occur as children grow-up and develop. It is of paramount importance for pediatric care providers to assess and interpret growth parameters in order to follow development and to establish if they are normally growing. As a matter of fact, a child's rate of growth and development reflects the health status.

In the first year of life, fundamental physical and developmental changes occur. During this time infants grow fast, tripling birth weight and increasing length of around 25 cm. Therefore, in this critical period of life anthropometric parameters need to be assessed frequently.

After this time, children grow slowly until puberty and usually it is necessary to perform growth assessment once or twice a year. By the end of the first year of age physical growth rate slows in association with a related decline in nutritional requirements.

Throughout middle childhood, and particularly between the ages of 6 and 12 years, children grow discontinuously with alternation of slightly slower growth and growth spurts. Finally, between the ages of 10 and 20 years, children experience rapidly biological and psychological changes leading to adolescence and adulthood.

In order to promote healthy growth, the earlier in life that children develop a healthy lifestyle, the better. Therefore, living in satisfactory hygiene conditions and having good habits and behaviors, such as eating healthy and being physically active, are crucial to ensure optimal development for children.

Action strategies and interventions designed by World Health Organization (WHO) to promote healthy growth include high-quality maternal nutrition and no smoking before and after delivery, absence of significant morbidity, exclusive or predominant breastfeeding from birth for at least 4 months, introduction of complementary foods by 6 months of age and continued breastfeeding to at least 12 months of age, and healthy environments. These WHO standards provide a good tool to monitor the rapid and changing rate of growth in early infancy regardless of ethnicity and socioeconomic status.

However, in developing countries it is not possible to guarantee a healthy lifestyle due to the well-known poor life conditions. Children living in resource-deprived settings are victims of the economic crisis and it is really difficult to ensure an optimal growth and development. The number of child mortality rates are increasing because of severe malnutrition, poor hygiene conditions, and infections. In Sub-Saharan Africa undernutrition is a leading factor underlying child mortality and morbidity, and contributes to 2.2 million deaths and a fifth of all disability-adjusted-life-years lost worldwide for children under the age of 5 years.[23] Therefore, in developing countries action strategies and programmes are needed to reduce neonatal mortality and to avoid nutritional depletion and related long-term effects.

Physiology of Puberty and Adolescence

Puberty is the stage of human development during which sexual maturation occurs and individuals become potentially fertile.[22] Typically, the onset of puberty occurs during adolescence, which represents a crucial period of life characterized by rapid physical, cognitive and social changes allowing children to transit from childhood to adulthood.

Hypothalamic-Pituitary-Gonadal (HPG) axis is inactive during pre-pubertal age, corresponding to period from early childhood to about 8-9 years of age. Low luteinizing hormone (LH) secretion occurs during sleep in a pulsatile manner, reflecting endogenous intermittent release of gonadotropin-releasing hormone (GnRH). During night-time, LH levels gradually increase as puberty approaches. Puberty begins when the sensitivity of the pituitary to GnRH increases, with pulsatile release of GnRH and increased overnight gonadotropins [follicle-stimulating hormone (FSH) and LH] levels. Gonadotropins induce enlargement and maturation of gonads and stimulate sex hormones production with development of secondary sexual characteristics.

The described endocrinological changes lead to progressive physical changes corresponding to the five pubertal stages according to the criteria of Tanner.

Usually, girls enter puberty between the ages of 8 and 13 years and the first physical sign is appearance of breast buds, although pubic hair may also appear. Under the influence of estrogens, secreted by the developing follicles in the ovaries, uterus enlargement occurs and endometrium proliferates. Subsequently, menarche occurs after two years, typically during breast stage IV, about one year after beginning of growth spurt. Normally,

growth acceleration begins in early adolescence, with girls experiencing peak of linear growth velocities during breast stage II. The average menarcheal age is 12.5± 1.0 years, with onset of menarche related to the degree of skeletal maturation more than to chronological age.

It has been reported that black girls undergo menarche earlier than do white girls. The reasons for these racial differences in timing of menarche are uncertain, however it seems to be influenced by genetic factors as well as environmental factors such as degree of fatness, nutritional status, strenuous physical activity and chronic diseases. In particular, energy balance is strictly associated with activity of GnRH pulse generator and the mechanism starting and sustaining puberty, possibly through hormonal signals originating from the adipocytes. In fact, in developed countries menarche occurs earlier than do in poor countries, likely due to satisfactory environmental conditions and healthy nutritional status.

In boys puberty starts at around the age of 9 years, with gradual enlargement of the testicles and thinning and reddening of the scrotum. A testicles volume of 4 cm^3 represents the first physical sign of puberty. Subsequently, penis and testicles progressively grow together with pubic hair. Other changes occurring during boys' puberty include voice, skeletal, muscular, and reproductive changes. In boys the pubertal growth spurt occurs typically 2 years later than girls and linear growth continues for another 3 years.

Physical maturity is generally reached by the age of 15 in girls and by the age of 17 in boys, with adolescents becoming sexually active.

Classification of Growth Disorders in HIV Infected Subjects

Growth faltering may adversely affect quality of life, especially once they reach adolescence and this should be taken into account when making decisions about starting and changing ART.[24]

Weight loss is common in HIV/AIDS adults, whereas in children living with HIV postnatal growth is typically affected. As a matter of fact, alterations in body fat distribution and lipid, glucose, bone metabolism and endocrine dysfunctions that take place in HIV infection may place HIV infected children at increased risk for future morbidities.[25]

Infected children are estimated to be significantly shorter and lighter than uninfected children. Differences in weight and height between infected and uninfected children are not obvious at birth, but increase with age. In children and adolescents living with HIV height growth has been shown to predict survival, and, height velocity has been described as the growth index most closely related to disease progression, immune status and plasma viral load in children receiving ART. [26] This association has been indicated as independent of factors such as age, viral load and CD4+ cell count.

Differences in growth velocities among infected and uninfected children increase after 2 years of age for height and after 4 years of age for weight and are more marked in the latter.[24] Similarly, HIV infected adolescents have lower growth parameters than the normal population and this is associated with a worse prognosis, as well as delayed puberty.

Failure to thrive (FTT) in infants and children with HIV infection is defined as a reduced rate of weight gain and growth for age, moving downward more than 2 percentile lines from the curve on age- and gender-specific growth curves for height, weight, or weight-for-height when the child is below the 25th percentile at baseline.[27] Alternatively, FTT may be defined as a sustained deviation from a parallel curve for children who are below the 5th percentile.[6] Infants and children infected through blood or blood product transfusion manifested FTT as the first presenting sign associated with development of opportunistic infections or even preceding the diagnosis of AIDS by two years. A decline higher than 15 percentiles in height or weight-for-age on two successive examinations predicted the onset of other severe HIV related signs and often evolved into a wasting state (disproportionate decrease in weight for length).

FTT is frequent, develops early in life, associated with severe disease and predicts a short survival. Growth and skeletal retardation associated with HIV related disease are similar to those observed in children with protein and calorie malnutrition or chronic diseases. During illness, this may be ascribed to fever and acute catabolic state. However, FTT occurs even in illness free periods, probably because of scarce intake, gastrointestinal dysfunction, intestinal brush border defect and reduced carbohydrate absorption as well as central nervous system manifestations which impair appetite or deglutition. But FTT may continue even when intake and absorption are sufficient, thus raising the possibility that neuroendocrine dysfunctions have a pathogenetic role.[6]

HIV related wasting syndrome is defined as weight loss of 10 percent or more of body weight or deceleration in weight gain resulting in downward crossing of at least two percentile lines on the weight-for-age chart in a child older than 1 year or less than 5th percentile on weight-for-height chart on two consecutive measurements separated by more than 30 days plus chronic diarrhea or chronic fever.[6,25,28] These growth abnormalities are characterized by loss of lean body mass due to the much easier protein conversion into energy than turning fat to afford energy demands of the body.

Stunting is another relevant clinical manifestation of growth disorder in HIV infection and is defined as a declining height-for-age (Z-score below-2 SD) characterized by an apparently normal differentiation but diminished size. This altered statural growth pattern has been associated with notably shorter survival and generally, is prominent after 1.5 months in children with HIV who survive to 18 months of age, indicating a postnatal neuroendocrine insult rather than malnutrition.[29] As previously reported, in the developed world, compromised height growth is a greater predictor of HIV progression, although in low and middle-income countries malnutrition is widespread and weight is more often compromised than statural growth.

The main periods of life during which HIV related growth abnormalities can develop are:

- Maternal HIV infection and intrauterine growth
- Growth in infants born to HIV infected mothers from birth to 2 years of life
- Growth in infants born to HIV infected mothers from 2 years of life
- Growth in adolescents.

Maternal HIV Infection and Intrauterine Growth

Perinatal transmission of HIV is the primary cause of pediatric infections. Although in uterus HIV transmission can occur in the first trimester of gestation, the infection occurs more frequently late. Furthermore, most children born to HIV infected mothers become infected during delivery because of missed prevention strategies. However, continual efforts to reducing this type of transmission have been realized by making prevention and HIV screening for pregnant women, antiretroviral chemoprophylaxis during pregnancy, elective cesarean section and not breastfeeding.

It has been reported that generally HIV infected infants born to HIV positive mothers are shorter, thinner and with a smaller head circumference than uninfected HIV exposed infants or infants born to uninfected mothers. Although these evidences, suggesting that fetal HIV infection affects fetal growth, numerous studies have reported that mean birth weight and length are similar in HIV infected and non HIV infected children. However, particularly in regions where the epidemic is taking the highest toll and access to ART is limited, the growth pattern of children born to HIV infected women is often impaired. In fact, in Sub-Saharan Africa maternal HIV infection has been described to affect pregnancy outcomes adversely. Linear and ponderal growth retardation is severe in children who become infected as early as 3 months after birth, however the birth weight is not significantly affected due to the fact that the highest transmission takes place near/at delivery. On the other hand, findings of studies performed in industrialized countries, where confounding by other maternal factors is more of a problem, are less consistent. An increased risk of preterm birth and growth retardation, both prenatal and postnatal, has been reported in children exposed to maternal history of illicit drug use.

The use of ART during pregnancy is now standard of care to prevent mother-to-child HIV transmission. There is no effect on birth outcomes or subsequent growth of exposure to intrauterine prophylactic antiretroviral drugs. Furthermore, ART during pregnancy does not increase the incidence of infants who are small for gestational age (SGA), and overall immunological and virologic ART responses are similar in both HIV infected and non infected children during pregnancy.

Subsequent to being born, infected children have the tendency to weigh less when compared to uninfected HIV exposed infants, with growth patterns worsening as children grow. HIV itself has been associated with low birth weight or poor postnatal growth during first months of life. A study conducted in Rwanda has reported that intrauterine growth retardation, but not prematurity was related to HIV infection.[30] However, up to now it is not clear whether HIV positive mothers have a major risk to deliver preterm or SGA infants. In fact, there are different pattern of birth outcomes and subsequent growth because of different etiologies, such as socioeconomic status, maternal nutritional status, drug and/or alcohol use, and prenatal care.

Finally, maternal health status represents one of the most important factors in predicting whether a newborn will survive: if an HIV infected mother becomes ill and cannot take care for her baby, that child has a major risk for comorbidity and mortality, increasing further if the mother dies.

Growth in Infants Born to HIV Infected Mothers from Birth to 2 Years of Life

HIV infected infants born preterm or with low birth weight are significantly more stunted and wasted than their reference groups at all time points, though their rate of growth faltering is slower. Differences in weight and length of infected and uninfected children start to appear in the first months of life and at 6 months of age HIV infected children are 1 kg lighter and 2 cm shorter than the uninfected subjects.[31] Immunological status and infant infections are important predictors of early growth in children born to HIV positive women. In some studies among Sub-Saharan African children wasting becomes prominent after 1 year.[16] Nonetheless, although the effect on weight is disproportional, an effect on length is still severe in this cohort, 50 percent with length-for-age Z-score below –2 SD by 1 year. Growth faltering in weight, but not in length, has been reported in HIV infected children in Brazil, probably reflecting the background

nutritional deficiencies and the concomitant infections. In these settings, early and aggressive nutritional management in HIV infected infants should be a priority intervention associated with ART.

However, several studies have revealed no significant differences in growth when uninfected infants born to HIV infected mothers were compared to healthy control subjects. The European Collaborative Study (ECS) investigated growth patterns in the first years of life of HIV infected and uninfected children born to HIV positive women, reporting that HIV infected children grew significantly slower, with differences between infected and uninfected children increasing with age. In fact, between 6 and 12 months uninfected children grew 1.6 and 6.2 percent faster in height and weight, respectively, than infected children.[24] Moreover, growth patterns in asymptomatic infected children were similar to those with mild or moderate symptoms, while compared with these two groups combined, severely ill children had poorer growth at all ages.

Also between uninfected children born to HIV infected mothers no substantial difference in terms of growth was reported during the first six months of life. Additionally, recent reports have shown that ART during pregnancy do not affect somatic growth of children born to HIV infected mothers. In a large cohort of uninfected Spanish children born to HIV infected mothers, anthropometric parameters were detected during their first 18 months of life. The reported proportion of intrauterine growth restriction among non premature neonates was 19.8 percent, and children born to mothers that used illicit drugs weighed less (2752 ± 325g vs 3002 ± 435g); similarly, the weight of the children born to smoking mothers was significantly lower. On the contrary, no statistically significant differences depending on the ART received during pregnancy were found. However, although mean weight, length and head circumference of population at birth were lower than the Spanish standards, these differences were not statistically significant and disappeared at 18 months of age.[32]

Furthermore, in another recent study it has been reported that there is no increased risk for birth defects associated with any of the in uterus used ART in uninfected children born to HIV positive mothers. Immunovirological characteristics of the mother did not influence the proportion of birth defects, but anemia in the first trimester and the use of illicit drugs (or methadone) did; the most frequent defects were genitourinary and cardiac.[33]

Growth in Infants Born to HIV Infected Mothers from 2 Years of Life to Adolescence

Data for beyond age 4 years are more limited. Progressive stunting is more typical than wasting in postnatal growth. The ECS has used data from a large prospective European study, and compared it with the general British standard growth patterns in the first 10 years of life of HIV infected and uninfected children who were born to HIV infected mothers. They showed that growth faltering may be related to the social environment, and our finding that uninfected children have normal growth, which is unaffected by exposure to maternal HIV infection. Therefore, they concluded that in Europe the HIV infected population is more like the general population. Furthermore, no effects on anthropometric parameters or developmental function up to age of 4 years have been described in children exposed to antiretroviral drugs (azidothymidine). However, HIV infected children grow considerably slower and differences between infected and uninfected children increased with age. Between 3 and 4 years of age uninfected children grow an estimated 10.7 percent faster in height and 10.8 percent in weight than infected children, whereas between 8 and 10 years of age these data become 16 and 44 percent in height and weight, respectively. Finally, by 10 years of age uninfected children an estimated 7 kg heavier and 7.5 cm taller when compared to HIV infected children.[24] Growth patterns in asymptomatic infected children are similar to those with only mild or moderate symptoms, however those who are severely ill have poorer growth at all ages.

Growth failure, principally regarding the height, may adversely influence the child's quality of life, especially during adolescence. Further studies are needed to clarify the correlation between ART and improved growth, in particular about different treatments and the best time of starting, in order to optimize growth of children living with HIV.

Puberty in HIV Infected Children

Virtually all children with chronic illnesses present with delayed puberty, which is associated with delayed growth and pubertal growth spurt. Late onset of puberty has been described in children with leukemia and renal failure, as well as in hemophiliac children who were infected with HIV by blood products. In fact, in both girls and boys living with HIV infection, breast development, genital maturity, and pubic hair growth occur later. HIV infection seems to affect production of hormones that directly regulate pubertal development and the earlier the onset and severity of disease, the greater is the negative effect on pubertal growth.

Ages at entry into Tanner stages in children with perinatal HIV infection have been defined. In a multicentre longitudinal study, 212 perinatally HIV infected children were followed up during puberty and compared with healthy controls. Ages of girls at P2, P3, P4, B2, B3 and B4 stages were >97th percentile

(≥21 month delay) of controls, whereas ages of boys at P2, P3, P4, G2, G3 and G4 stages were at the 75th-97th percentiles (≤15 month delay).[34]

Delay in pubertal development seems to be not related to weight for height, age at onset of severe disease, extent of disease progression, treatment experience, and immune status. However, the effects of immune suppression have been recently assessed in the Pediatric AIDS Clinical Trials Group 219 protocol, where pubertal development of 983 perinatally HIV infected children was compared with those of HIV negative subjects in order to establish if immune suppression delayed puberty. Children were considered to have normal immune function if they had a CD4+ cell percentage < 25 percent and severely immune depressed if they had CD4+ cell percentage <15 percent. The authors reported that the girls became pubescent approximately one year before boys. The average age of puberty was 10.2 years for girls with good immune function and 10.9 years for girls with severe immune suppression. Similar tendency was detected in boys with puberty happening earlier (average 10.9 years of age in those with good immune function, and at 11.5 years in those boys with severe immune suppression). In addition, in a longitudinal analysis, also higher body mass index and being of black race were associated with earlier onset of puberty in girls, while Hispanic and/or African-American origin and use of protease inhibitors were associated with earlier puberty in boys.[35]

Recent data confirm these findings, reporting delayed sexual maturation in perinatally HIV infected children in relation to immune status. In fact, females with severe immunosuppression (CD4+ percent <15) were significantly less likely to enter adrenarche and puberty when compared to not immunosuppressed females (CD4+ percent >25); similarly among males, those with severe immunosuppression were significantly less likely to enter adrenarche and tended to be less likely to start puberty (than not immunosuppressed males).

The HIV related endocrine dysfunctions determine anxiety and feelings of being different. As reported, the main concern for HIV infected adolescents between ages of 13 and 17 years in Côte d'Ivoire was represented by abnormal physical development; girls with delayed puberty could not participate in traditional rituals and were worried that they could never marry or have sons. Other girls were worried with signs of HIV infection, such as weight loss, which could indicate their serostatus.[36]

Overall, health care workers managing adolescents perinatally HIV infected need to deal with psychological issues coming from delayed puberty.

Reproductive Health of Adolescent Girls Perinatally HIV Infected or with Behaviorally Acquired HIV Infection

A growing number of children who acquired HIV infection at birth now have reached adolescence becoming sexually active. In fact, apart from comorbidities associated with HIV infection and adverse side effects and long-term toxicities associated with ART, the majority of youth who are living with HIV have good opportunities of surviving into adulthood.[37] Therefore, it is of utmost importance to guarantee essential supportive and behavioral programs for adolescents for their well-being as well as to reduce sexual risk factors.

It is well known that HIV infection frequently leads to progressive changes in psychosocial and cognitive disorders. Several studies have evaluated reproductive health outcomes for adolescents with perinatal HIV infection. In particular, recently it has been reported that around 40 percent of adolescents HIV infected have not communicated their serostatus to the partners or engaged in unprotected sexual intercourse, increasing sexual risk of transmission.[38] For this reason, promoting protected sexual behaviors by HIV positive adolescents with their partners is crucial. Further, a high risk of genital infections, such as papillomavirus infection or cervical squamous intraepithelial lesions, have been documented in adolescents and young women infected with HIV through sexual activity or illicit drug use.

Regarding reproductive health in adolescents perinatally infected with HIV, up to now just few data are available. Several studies have evaluated pregnancy outcomes in perinatally HIV infected young women. A recent study in India has reported that pregnancy seems to be not related to adverse maternal or fetal outcome in perinatally HIV infected adolescents and young adults if ART is taken consistently before and during the gestation. Recently, in a cohort of 174 perinatally HIV infected teens it has been reported that 17 percent of girls experienced a first pregnancy by 19 years of age and nearly half had abnormal cervical cytology, suggesting the strong necessity for better provision of reproductive health services such as contraceptive counselling and cervical cytological screening. It is unsettling that Pap tests have been performed by just half of the sexually active participants.[39] In the same study of teens aged 15 to 19 years, the pregnancy incidence rate was lower than that reported for predominantly HIV uninfected girls of similar age in the United States in 1999 (33.5 per 1000 versus 86.7 per 1000 person-year).[40] Further, the reported rates of genital infections such as trichomoniasis, chlamydial infection, and gonorrhea were lower than

those detected in the Reaching for Excellence in Adolescent Care and Health (REACH) cohort, which comprised of girls HIV infected during adolescence most likely through sexual intercourses.[41] The prevalence of abnormal cervical cytology was 29.7 percent, which is lower than the prevalence of 56.4 percent documented among 133 girls infected with HIV in adolescence in the REACH cohort. The reported prevalence could reflect an increased susceptibility to HPV and other infections in the perinatally HIV infected girls.

These findings highlight the importance of obtaining sexual histories, providing counselling to prevent unintentional pregnancies, screening for genital infections, performing regular Pap tests and managing cervical lesions.

It is time to pay attention to reproductive health of teens and young adults living with HIV in order to educate them on safer sexual activity. Adequate counseling and sustainable interventions should become an integral part of overall approach to helping adolescents live as normal a life as possible.

Pathogenesis of Impaired Growth

The pathogenesis of HIV related growth failure is complex. Studies conducted largely in industrialized countries have identified multiple factors involved in growth failure in HIV infected children. These include endocrine dysfunction, alterations in gastrointestinal function, malnutrition and chronic or recurrent infections.[21] All of these conditions are preventable, reversible or modifiable. Furthermore, whether impaired growth is an independent HIV symptom or whether it is indirectly caused by other HIV clinical manifestations is not yet completely understood. As a matter of fact, levels of HIV RNA are lower in infected children with normal rates of growth than children with compromised growth. Suppression of HIV viral replication has been shown to have a favorable effect on growth.

The Role of Endocrine Dysfunctions

A number of neuroendocrine abnormalities with the potential to affect growth were identified in HIV infected children, although no single endocrine abnormality is consistently encountered in HIV associated growth failure.[21] A role of GH dysfunction has been suggested among causes of HIV associated growth retardation. Children differ from adults in such a way that they tend toward developmental retardation and failure of somatic growth with occasional immunosuppression. Deficiencies in GH and IGF-1 levels have been seen at all clinical and immunological stages of disease, but are most pronounced in advanced cases. Therefore, early HIV infection may cause endocrine dysfunctions characterized by dysregulated GH secretion. Decreased GH secretion has been reported in children not on treatment, but primary GH deficiency has been identified only occasionally. The circadian secretory pattern of GH and stimulated GH levels are normal in the great majority of children with HIV infection. Because of the episodic pattern of GH secretion, incidental GH concentration measurements provide inadequate information about the amount of GH secreted over a longer period. Similarly, IGF-1 has variably been reported as normal or reduced. In children with wasting syndrome and/or active disease, acquired GH resistance is seen, with increased GH levels and decreased concentrations of IGF-1. Therefore, the expected GH-induced increase in IGFBP-3 is blunted. On the other hand, it has been suggested an enhanced proteolysis of IGFBP-3 to be associated with FTT. In experimental studies, the infusion of HIV glycoprotein 120 (gp120) into the rat brain caused release of interleukin 1 or tumor necrosis factor, which suppressed GH and GHRH at high concentration. Furthermore, the envelope protein gp120 at its low concentration causes death of neurons by indirect mechanism, in addition to slowing/preventing the appearance of developmental milestones in neonatal rats. A similar mechanism could be taking place in HIV infected children.

Moreover, there is a close sequence homology between a 5-amino acid epitope of GHRH [the homologous peptides vasoactive intestinal peptides (VIP) and signalling molecule (PACAP)] and peptides derived from the V2 region of the gp120 molecule, which suggests that gp120 could compete for GHRH and VIP receptors, potentially contributing to GH suppression. A recent study demonstrated that the gp120 antagonist D-Ala-Peptide-T-Amide (DAPTA), when co-administered with gp120, is able to prevent the GH suppression, suggesting that the effects of gp120 at the level of the hypothalamus may occur through suppression of VIP receptor-mediated GHRH release. Because VIP can stimulate GHRH release from the hypothalamus, it is also possible that gp120 blockade of GHRH and/or VIP on their pituitary receptors could further inhibit secretion of GH, hence poor growth.

There is also an association between GH concentration and lipodystrophy, in patients receiving ART. On the contrary, normal GH secretion has been reported in otherwise healthy HIV infected patients, without demonstrated wasting or lipodystrophy. Although the mechanisms of these changes in fat redistribution have not been elucidated, recent data suggest a strong inverse correlation between increased visceral fat and reduced GH concentrations. The ART-associated lipodystrophy syndrome has not been extensively studied in children, but it occurs more often than thought, although the manifestation is less severe than in adults. The entire

spectrum of morphologic and metabolic derangements reported in adults has also been described in HIV infected children and adolescents. It has been shown that recombinant human GH (rhGH) therapy reduces the abdominal and dorsocervical fat in addition to improving lipid profile and lean mass in HIV infected adults with abnormal fat accumulation. These changes are related to an overall satisfactory increase of IGF-1 which may improve in children. These facts give an initial proof that the use of rhGH may be an advantageous treatment strategy for pediatric lipodystrophy. GH treatment has a lipolytic action; however, the duration of ART can contribute to peripheral lipoatrophy as described in HIV infected children.

A study performed on adult patients using GHRH showed a reduction of visceral adipose tissue (VAT), a significant reduction in VAT/subcutaneous adipose tissue (SAT) ratio during treatment, and no worsening of peripheral lipoatrophy. Additionally no substantial changes in GH secretion were observed during the trial with GHRH. These results may suggest that GHRH supplements could be efficient to accomplish VAT reduction without a reduction in SAT. Further studies are therefore necessary in HIV infected children for a clear picture on the risk/benefit of rhGH therapy in pediatric lipodystrophy.

Protein malnutrition, one of the features of HIV infected children, is linked to combined GH and IGF-1 resistance. In addition, serum IGF-1 levels are low despite IGF-1 resistance. This obvious paradox may arise directly from contemporaneous GH resistance or result from the ability of undernutrition to overrule an increased serum IGF-1 levels, which might be predicted based on standard negative feed-back, as usually occurs with ligand when there is reduction of receptor activity and/or reduction in down-stream post receptor function. Resistance to GH, IGF-1, and other growth factors have been suggested as a potential cause for growth failure in children with pediatric HIV infection. Both normal and low serum IGF-1 levels have been described in HIV infected children and adults; however the effect is more pronounced in children with FTT. Additionally, low levels of IGFBP-3 and acid-labile subunit, members of the circulating ternary complex, have been reported to be low in poorly growing children with HIV infection and these children tend to have increased IGFBP-3 proteolysis, as seen in other hypercatabolic states. The mechanism by which IGF-1 resistance develops in children with symptomatic HIV infection could be linked to the augmented production of cytokines which occurs in patients with AIDS. If the mechanism for the GH and IGF-1 resistance in children with symptomatic HIV infection involves the IGF-1 receptors (IGF-IR), one might also anticipate resistance to supraphysiological concentrations of insulin, the action which is normally mediated through the IGF-IR. Existence of circulating inhibitors of IGF-1 action may possibly explain resistance to GH and IGF-1 without resistance to supraphysiological concentrations of insulin, one of the mechanisms being increased production of IGFBP.

Another concern is the occurrence of an excessive accumulation of intra-abdominal adipose tissue (IAT) in HIV infected children with overt signs of lipodystrophy and this is associated with longer duration of ART. The optimism generated by overall improving health among patients on ART has been tempered by concerns that these therapies may be associated with adverse metabolic effects, such as insulin resistance (IR), hyperlipidemia, and changes in body composition. It has been demonstrated that the degree of body fat was associated inversely with indices of GH secretion and free fat acids (FFA) remained negatively associated with peak GH response to GHRH. Similarly, GH response to GHRH has been improved in patients using a niacin derivative used as a hypolipidemic agent called acipimox, suggesting that FFA may play an inhibitory role with respect to GH secretion in the HIV lipodystrophy. Furthermore, FFA have been found to increase in the lipodystrophic patients, with increased GH response to GHRH in relation to decrease in FFA after acipimox administration. This suggest that increased FFA inhibit GH response to GHRH in lipodystrophic patients. Previous studies in HIV lipodystrophic patients with visceral adiposity demonstrated increased FFA and lipolysis rates. Changes in fat redistribution may occur due to HIV itself or exposure to ART. There are different mechanisms leading to decreased GH, IR, and increased FFA in these patients: some of these mechanisms include somatostatin one, reduced GH response to GHRH, and decreased ghrelin. Consequently, decreased GH may contribute to visceral adiposity and IR, creating a vicious cycle of metabolic dysregulation. Additionally, altered GHRH pulsatility or GH responsivity to GHRH at the pituitary lead to a decrease in GH release. A number of studies have suggested that the mechanism by which the increased amounts of FFA may cause blunted GH secretion is by increasing endogenous somatostatin tone. However, studies performed in animals suggest that FFA impaired GH release directly at the pituitary gland. It is likely that excess FFA may alter GH secretion in severe lipoatrophy without visceral adiposity. Another mechanism for the reduction of GH release in HIV infected patients is reduced ghrelin. In adult HIV infected patients with lipodystrophy ghrelin is reduced and this was associated with reduced mean GH pulse, GH secretion, and increased insulin, suggesting that increased somatostatin and excess FFA impair GH response to GHRH. GH reduction is also seen in obese non-HIV

infected patients, as well as reduction of GH indices. HIV lipodystrophy on the other hand is unique, in those patients without severe generalized obesity, but displays fat redistribution, in such a way that total fat is not increased. Visceral adiposity is a significant predictor of GH deficiency/resistance in HIV infected patients. IGFBP-3 proteolytic activity is a beneficial response to stress/injury, hence reduction of IGFBP-3 affinity to IGF-1 conserves a positive nitrogen balance on the expense of growth in HIV infected children. Thus, the proteolysis of IGBP-3 has a direct impact on linear growth of HIV infected children.

These studies suggest a complex representation whereby alterations in insulin and fatty acids affect GH secretion in HIV lipodystrophy, a phenomenon which may apply to children and impair growth. Consequently, GH has important effects on fat metabolism in both children and adulthood and GH replacement may lessen health risks associated with increased adiposity. Some studies have shown weight gains with rhGH, plus recombinant human IGF-1 or GH only administration. rhGH reduces excess accumulation of IAT in lipodystrophic HIV infected adults, while data in pediatric patients is still scarce; it has been showed that rhGH in HIV infected adolescents reduces IAT, trunk, and also limb fat, while increasing lean mass. Overall short-term rhGH is well tolerated and is not associated with worsening of glucose and lipid metabolism, but data are lacking on chronic use of GH in children. The evidence that GH levels are suppressed with HIV infection together with reports that exogenous GH ameliorates AIDS-associated wasting suggest that HIV infection or viral proteins disrupt endocrine function, leading to diminished GH production, which in turn contribute to growth impairment in children.[21]

In summary, the growth promoting agents that can be effective in HIV infected children should have inhibitory factors on IGFBP-3 proteolysis and be able to increase the concentration of IGF-1. Similarly, drugs that block the GH suppressing actions of gp120 like DAPTA should be considered for their potential therapeutic efficacy by their ability to normalize endogenous GH levels.

Abnormal thyroid function test results are common among HIV infected adult patients. The prevalence of overt thyroid disease does not appear to be significantly increased in HIV infected patients. Estimates of the occurrence of primary and secondary thyroid abnormalities vary widely from 18 percent to none. It is possible that abnormal thyroid function can contribute to the growth retardation often present in children with HIV infection. Suggested causes for impaired thyroid function in HIV patients include starvation and debilitating illnesses, direct evidence of thyroid tissue infection by the virus, immune reconstitution syndrome and nonthyroidal illness associated with advanced stage of the HIV infection.

Alterations in Gastrointestinal Function

Under nutrition plays a big role in HIV associated growth failure.[25] However, even in settings where food sources are adequate and readily accessible, dietary intake is lower in HIV positive children than HIV negative controls. Furthermore, gastrointestinal infections and malabsorption of carbohydrates, fat and protein have been commonly described, although a detrimental effect of these conditions in such a way to determine impaired growth has been not demonstrated. Comorbid conditions which impair food intake like oral candidiasis contribute in reduced food intake, as well as the increased level of tumor necrosis factor-α which could be involved in appetite inhibition.

Despite normal rates of resting and total energy expenditures, the energy balance deficit found in HIV infected children suggests that the dietary intake is not enough to meet the metabolic demands and sustain growth. Improvement of dietary intake alone does not improve linear growth and lean body mass, however there is improvement in weight. Dietary intake also varies inversely with level of virus, suggesting that viral replication directly or indirectly suppresses appetite. The temporal relationships between growth and viral load are uncertain. A recent study reported no association between growth at 24 weeks and viral load at 12 weeks after starting therapy with azidothymidine, dideoxyinosine or both.[42]

HIV infected children have micronutrient deficiencies which have adverse effect on growth. For instance, vitamin A deficiency was found to influence ponderal and linear growth in HIV infected children during the first year of life. Glutathione, the principle intracellular antioxidant, was reported to be reduced in children with HIV infection, with lowest concentration in children with growth failure. Use of cysteine and N-acetyl cysteine for restoration of glutathione stores has been advocated.

Furthermore, anemia associated with a deficiency of iron has been described in HIV infected children.[19] This condition represents one of more important HIV related comorbidities. As a matter of fact, it has been reported a significant high prevalence of anemia in subjects living with HIV, especially in children living in rural settings. In particular, recent data have indicated an increased prevalence of anemia in stunted children, although also underweight children have a high risk to be affected. The high prevalence of anemia is due to many factors, such as nutritional deficiencies, opportunistic infections,

parasitic infestations and chronic infections. Each of these factors can act leading to depressed erythropoiesis. As recommended by WHO, asymptomatic children living with HIV need a 10 percent increase in energy intake. Symptomatic children need further increase of 20-30 percent, while children experiencing weight loss need a further increase of 50-100 percent.[43] Up to now there is no clear evidence to base recommendations of iron supplemen- tation in HIV infected children in reducing risk of anemia. The beneficial effects with ART on reducing anaemia has been reported. In a study performed in South India, a significant increase in hemoglobin and weight gain have been reported in HIV infected children after 6 months of starting ART.[44]

Diarrheal Diseases and Malabsorption

Diarrheal diseases are common causes of childhood malnutrition and growth retardation. However, they contribute significantly to poor growth in HIV infected children. It has been hypothesized that the effects of diarrheal morbidity on growth faltering may be more severe or more common in HIV infected children. A potentially important mechanism by which vitamin A affects growth is by preventing diarrheal and respiratory illnesses.

Infections by Cryptosporidium species represent a major cause of severe diarrhea in developing countries, mainly affecting children and untreated subjects living with HIV infection. However, until introduction of ART a relatively high prevalence of this infection has been reported also in developed countries. Data from India reported that prevalence of cryptosporidial diarrhea in adults living with HIV ranged from 0.7 to 83 percent in symptomatic and from 1.4 to 57 percent in asymptomatic subjects, while the prevalence in children ranged from 1.1 to 18.9 percent.[45] The common cryptosporidial species affecting children living with HIV in India are *Cryptosporidium hominis* and *Cryptosporidium parvum*. A few studies from India have identified a correlation between low CD4+ count and symptomatic cryptosporidiosis.[46] In fact, Cryptosporidium is self-limiting in subjects with normal immune function, but it can be severe in immune depressed and malnourished individuals. Up to now no therapies are satisfactory to treat *Cryptosporidium diarrhea*. Other enteric pathogens are represented by *Giardia lamblia, Mycobacterium avium-intracellulare, Clostridium difficile, Salmonella, Shigella, Campylobacter, Cytomegalovirus, Adenovirus, Rotavirus,* and *Herpes simplex virus.* Diarrheal diseases and malabsorption worsen growth pattern of children and adolescents living with HIV. In fact, intestinal epithelial cell alterations cause malabsorption and, consequently, malnutrition and weight loss due to nausea, vomiting, pain and fever. These stressful events lead to immune dysfunction and metabolic abnormalities such as low T cell and CD4+ number, impaired antibody responses and cytokine production.

Pathogenesis of Impaired Sexual Maturation

In HIV infected children, delay in the onset of puberty is the result of GH dysregulation, hypothyroidism, and testosterone reduction. The earlier the onset and severity of disease, the greater the negative effect on pubertal growth.[21] Moreover, HIV infection has been associated with HPG dysfunction. The HPG axis is profoundly affected in calorie protein energy malnutrition which is a feature of HIV infection, hence there is reduced growth with consequent delayed puberty. Malnutrition inhibits gonadotropin secretion, probably via an effect on LHRH neurones which can result in gonadotropin deficiency. The pubertal delay relates both to the infection itself and ART, consequently children show height-weight and pubertal retardation. A longitudinal study in transfusion-infected boys found that age-adjusted testosterone levels decreased with decreasing in immune function and subsequently, delayed pubertal development and growth failure. Adolescents may be particularly vulnerable to hormonal changes because the HPG axis has not yet fully matured.

Delayed puberty is more pronounced in females than males, probably due to the difference in the sensitivity of pituitary to GnRH. FSH and LH levels are low or normal, suggesting a central component of the hypogonadism. In advanced disease, testosterone levels are low as a result of both gonadal and extragonadal factors that contribute to testicular dysfunction. An increment of plasma HIV RNA has been associated with decrease in testosterone levels, an effect which is more pronounced in children with high viral load and decrease in CD4+ count.

Different studies have shown that children with perinatal HIV infection have delayed puberty associated with the severity of the disease. Part of the linear growth failure could be attributed to the delay in puberty. The hemophilic growth and developmental study investigated the relationship between HIV associated immune dysfunction and puberty; their findings showed a significant delay in pubertal development associated with increasing levels of immune dysfunction.

The euthyroid sick syndrome accompanied by increased basal thyrotropin levels, free thyroxine levels, low IGF-1 and IGFBP-3, due to proinflammatory interleukin production triggered by HIV may be the mechanism leading to delayed sexual maturation.[21]

The timing of sexual maturation is also determined by the interaction of inheritance with several environmental factors, such as family size, socioeconomic status, living in rural or urban communities, or living at high altitudes. Furthermore, pubertal delay may represent the result of parental ill-health and bereavement due to illicit drug use in the parents and the consequent risk of neglect. Indeed, it is important to consider that there are now sizeable cohorts of perinatally HIV infected children who are approaching adolescence. Most of them will fail to reach the height of their peers and their physical appearance will exacerbate their feeling of being both different and sick. Part of the linear growth failure could be attributed to the delay in puberty they suffer.

A deeper knowledge of the mechanisms which lead to a delayed puberty could guide development promoting strategies saving much psychological suffering to these adolescents. Furthermore, better understanding of the mechanisms leading to delayed puberty in girls and boys with perinatally acquired HIV infection might lead to appropriate treatment when required.

Conclusion and Future Developments

A dysregulation of the hypothalamic-pituitary axis, toxic or allergic drug reactions may play a role in endocrine dysfunction in HIV infected children. These dysfunctions require an endocrine function monitoring, since they have relevant effects on growth and pubertal development. A better understanding of the mechanisms leading to growth impairment and delayed puberty in children with perinatally acquired HIV infection might lead to appropriate treatment when required. There is a need for deeper knowledge about the mechanisms leading to delayed puberty which could direct development promoting strategies. Further studies are warranted to investigate the mechanisms leading to delayed puberty.

It is fundamental that pediatric care providers and pediatric endocrinologists should implement appropriate preventive screening and therapeutic strategies, including good adherence to lifelong regimens and care of reproductive health during childhood and adolescence, in order to maximize survival and quality of life in infants, children and young people living with HIV.

Case Studies

Case 1

- Larry is a 13 months old baby
- He was admitted to the hospital pulling at his right ear
- Furthermore, he appeared underweight.

History

- Larry was born in a rural hospital in Uganda
- He recently moved to town with his family to find a job. The HIV status of his parents was unknown because they did not have their 'Road to Health' cards.

Clinical Characteristics

- Larry's parents agreed to be tested for HIV infection and, unfortunately, they were positive
- The child was started on cotrimoxazole prophylaxis. Because at the moment no virologic tests were available, the consultant decided to test him at 18 months of age
- However, two months later Larry was again admitted to the hospital with four possible presentations that prompted to perform earlier HIV test.

Situation 1

Larry presented with a 4 days history of diarrhea and vomiting. Clinic examination: dry mucous membrane and sunken eyes.

Situation 2

Larry presented with a 6 days history of cold, cough and fever.

Situation 3

Larry presented with appetite loss and weight loss of 3 kilograms since his last visit two months ago. His mother provided a poor dietary history.

Situation 4

Larry's parents have noted that the baby was no longer crawling. Furthermore, he presented irritability and muscular hypotony.

Situation 1. Diarrheal illnesses

Larry presented with a 4 days history of diarrhea and vomiting. Clinical examination: dry mucous membranes and sunken eyes.

- How would you manage him?
- When would you give antibiotics?
- When would you follow up?

Situation 2. Respiratory illnesses

Larry presented with a 6 days history of cold, cough and fever.

- How would you manage him?
- When would you give antibiotics?
- When would you follow up?

One month later, Larry returned to the hospital with night sweats, pallor, appetite loss, weight loss and persistent cough.

What would you now suppose?

Tuberculosis (TB) may be suspected. Therefore, look for history of TB contact.

Do tuberculin test: Mantoux test and read it after 48-72 hours.

Refer to the higher level facility to investigate Larry if you are at higher level.

Situation 3. Nutritional support

Larry presented with appetite loss and weight loss of 3 kilograms since his last visit two months ago. His mother provided a poor dietary history.

Give his parents nutritional recommendations.

However, three weeks later Larry returned to the hospital with asthenia and ongoing weight loss.

I. What would you now suspect?
II. What do you believe is the cause of his symptoms?
III. What would your management strategy be?

Situation 4. Neurologic manifestations of HIV

Larry's parents have noted that the baby was no longer crawling. Furthermore, he presented with irritability and muscular hypotony.

I. What do you now suspect?
II. How would you manage him?

Case 2

- Brenda is a 5-year old girl
- She presented to the hospital with a 3 days history of diarrhea and vomiting.

History

- Past medical history: Recurrent respiratory infections and poor growth
- Brenda's mother tested negative for HIV infection during her pregnancy, as documented on her "Road to Health" card.

Clinical Characteristics

Clinical examination: Vitals signs were within normal limits and she was alert and oriented. However, the patient was 6 percent dehydrated and she presented the following clinical signs: dry mucous membranes, sunken eyes, pallor, lymphadenopathy, hepatosplenomegaly and oral candida.

We obtained consent to test Brenda for HIV infection and the test was positive.

Clinical Question

Besides mother-to-child transmission of HIV, what other routes of transmission exist in children, who test positive, born to HIV negative mothers?

It is significant to note that although we tested Brenda, her mother was not retested. It is probable that she was HIV positive and that laboratory or human error accounted for this incongruity. The chance of Brenda testing negative and not acquiring the virus from her mother is unusual because perinatal transmission of HIV infection represents the most common route of transmission. However, factors which could be responsible for her status could be past blood transfusion/parenteral injection during previous hospital admissions or sexual abuse.

Case 3

Eleen is a 16 year old girl.

She was admitted to the hospital with a 20 days history of headache, arthralgias, myalgias and fever. When asked, she admitted to have recently had unprotected sex.

History

Previously healthy girl.

Clinical Characteristics

At hospital admission, she was oriented with a normal level of consciousness and responded appropriately to questions.

Her head, ear, heart and lung exams were normal. Her oral exam was significant for thrush.

She also presented lymphadenopathy and hepatosplenomegaly.

Laboratory Investigations

- Laboratory studies showed complete blood count: hematocrit 46 percent, hemoglobin 12.5 g/dL, white blood cell count 12,500 cells/L (neutrophils 94%, lymphocytes 3 percent, monocytes 1%, atypical lymphocytes 2%), and 177,000 platelets/L.
- Serum transaminases elevated.
- Tests for Cryptococcus antigen, Toxoplasmosis antigen, Epstein Barr virus IgG and IgM, Cytomegalovirus IgG and IgM, Herpes Simplex virus polymerase chain reaction (PCR), cultures for tuberculosis and fungi on plasma and cerebrospinal fluid (CSF) samples were all negative. However, CSF analysis showed 24 white blood cell count, 94 percent lymphocytes and 6 percent polymorphonuclear leukocytes (PMNs); the CSF protein was slightly elevated.

- HIV enzyme-linked immunosorbent assay (ELISA) was performed resulting negative. However, because her symptoms and laboratory exams were consistent with HIV infection, plasma viral load determination (PVL) was performed resulting positive.

Diagnosis

Eleen was recently infected with HIV and her symptoms progressively improved, after beginning treatment with antiretroviral drugs.

Her clinical features were consistent with HIV aseptic meningitis and a mononucleosis like syndrome; this phenomenon is called "acute retroviral syndrome" and occurs from 2 to 8 weeks after initial exposure in up to 70 percent of the patients. The HIV ELISA tests can be initially negative. The decrease in the absolute lymphocyte count and elevated serum transaminases are common. CSF lymphocytic pleocytosis can be seen at any stage of HIV infection; it diminishes and protein elevation persists as HIV progresses.

In primary infection, virus replication in CD4+ cells intensifies prior to the initiation of a virus specific immune response, leading to a burst of viremia and subsequently to a rapid dissemination of the virus. Acute retroviral syndrome may last 3 days to 3 weeks and can include headache, arthralgias, fever, lymphadenopathy, maculopapular rash and sore throat, and some individuals experience neurologic involvement with possible cerebrospinal fluid pleocytosis. Generalized lymphadenopathy occurs in 35 to 60 percent of asymptomatic HIV infected persons.

In most centers, the primary screening test is represented by ELISA. If the test is reactive, it is repeated in duplicate and if either or both repeat tests are reactive, the sample is considered positive and a western blot or indirect immunofluorescence assay is done on the sample for confirmation. The western blot detects antibodies to specific denatured HIV-1 proteins. The absence of all bands in western blot is considered a negative test. This protocol has a 3-4 week "window period" prior to seroconversion, during which results can be negative or indeterminate. Most experts suggest the use of PVL for patients that may be in the window period as in this case history. In addition to PVL, very sensitive virologic assays (RT-PCR, bDNA) are also used for diagnosis.

Key Messages

- Poor growth observed in vertically HIV infected children should be interpreted in the context of their social environment. Since growth seems to be one of the most sensitive indicators of the disease progression in children living with HIV/AIDS, children with HIV infection should be assessed in terms of growth
- With improved long-term survival, continued follow-up is necessary to evaluate the effects of prolonged use of ART on potential adverse events, immune function, growth, sexual maturation and quality of life in this young population
- HIV infected children with advanced disease should undergo periodic evaluation including thyroid function, growth hormone levels, IGF-1, IGFBP-3 and androgens, in order to identify subclinical endocrine dysfunctions
- Growth failure in HIV infected children is multifactorial including diet, social context, endocrine and metabolic dysfunctions
- Poor growth is both a manifestation of HIV as well as an independent risk factor for death.
- The growth assessment of HIV infected children is important both to determine the disease stage and prognosis and the effectiveness and toxicity of ART regimens, and to study the nutritional, endocrine and metabolic implications of the infection and treatment
- Physicians should be alert to the possibility of wasting in HIV infected patients receiving ART and should consider rhGH in the treatment to improve patients' growth and quality of life.

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2.12

Malignancies Associated with Pediatric HIV Infection

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Introduction

According to the UNAIDS 2008 global report on AIDS, at the end of 2007, approximately 33 million adults and 2 million children were living with HIV infection.[1] According to their 2006 Epidemiology Report on the Indian AIDS epidemic, at the end of 2005, approximately 0.8 percent of the adult population in India was living with HIV infection. Six of India's 35 states comprise 80 percent of AIDS cases in the country. Roughly 1 percent of India's pregnant women are reported to be HIV positive.[2] The successful use of antiretroviral drugs during the antenatal and perinatal periods in reducing vertical transmission to the infant, coupled with the use of highly active anti-retroviral therapy (HAART), has dramatically changed the face of pediatric HIV/AIDS in developed countries. Worldwide, children account for almost 14 percent of new HIV infections, but account for only 7 to 9 percent of cases being treated. Left untreated 50 percent of children with perinatally-acquired HIV infection die by two years of age.[1] In addition to a dysfunctional reconstituted immune system, decreased ability to clear oncogenic viral infections, and other unknown factors, may make this population more prone to the development of neoplastic diseases.[3]

Pediatric AIDS classification is based on the level of immune suppression as defined by percentage of CD4 cells (up to age 5 years) and diagnosis of an AIDS-defining illness.[4] AIDS-defining malignancies, are Kaposi's Sarcoma, Non-Hodgkin's lymphoma (NHL), and cervical cancer; however of these NHL / Burkitt's lymphoma are the most pertinent to the pediatric population. Kaposi's and cervical cancer are mainly relevant to adults with HIV/AIDS but with increasing numbers of perinatally infected children surviving to adulthood these will gain more relevance.

Non-AIDS defining malignancies that are seen at an increased rate in those with HIV infection include leiomyomas, leiomyosarcomas, Hodgkin's disease (HD), and lymphomas of mucosa-associated lymphoid tissue (MALT). We will provide an overview of the malignancies that are commonly observed in children with HIV/AIDS.

Several studies in both the adult and pediatric populations have assessed the risk of developing a malignancy if infected with HIV. Not only has it been determined that there is an increased risk, but also it has been shown that there are age and geographic distributions associated with the type of malignancies that are prevalent. Engels et al measured a cancer risk relative to the general population, defined as standardized incidence ratio (SIR), in both the pre- and post-HAART periods. They determined the risk declined in NHL from SIR 53.2 pre-HAART to 22.6, post-HAART. They also found increased risk in non-AIDS malignancies such has Hodgkin's disease.[5] Studies from Italy, Great Britain, the United States, and India have all determined that in the pediatric population there is an increased incidence of malignancies in HIV infected children, with the highest percentage of diagnoses being NHL ranging from 1.56 to 3.57 per 1000 person-years.[6,7] Of the 32 tumors found in 31 children in the Italian study, 24 (81%) were NHL.[7] In an observational study conducted in a tertiary cancer hospital in India between 2001 and 2007, 11 children were diagnosed with HIV and cancer. This constituted 2.3 percent of all patients diagnosed in that time period with both the diseases. NHL accounted for 81.8 percent of the diagnoses.[8] At our center,[9] we diagnosed 12 cases of malignancies from our cohort of approximately 200 children with perinatally acquired HIV/AIDS between 1992 and 2007. Of those 12, 9 were diagnosed with NHL, 2 with HD and 1 with leiomyosarcoma.

AIDS Defining Malignancies

Non-Hodgkin's Lymphoma (NHL)

Overview

Lymphomas are malignancies that arise in the lymphoid system. They are usually classified as NHL or HD. NHL can be further classified as lymphoblastic lymphomas, small noncleaved cell lymphomas (SNCCLs) or Burkitt lymphomas, or large cell lymphomas (LCLs). Clinically lymphomas may present as local disease all the way to overt leukemia, which is characterized by bone marrow involvement. NHL may be further divided into lymphomas of B, T or natural killer (NK) cell origin. Approximately 85 percent are the result of progressive clonal expansion of B cells.[10]

Clinical Presentation

NHL is grouped into subtypes based on clinical behavior. These are low, intermediate and high-grade. Low-grade lymphomas are usually confined to lymph nodes and extranodal disease is uncommon at presentation. The bone marrow is frequently involved and may produce concomitant cytopenias. Intermediate and high-grade lymphomas typically present with extranodal involvement and systemic symptoms. They may also present as masses in any location including with mediastinal involvement, which may compress vital structures, or present with signs of bowel obstruction.[11] SNCCL's or Burkitt's are most prevalent in equatorial Africa and may present as a mass in the jaw, nasopharynx or orbit. In children, the clinical presentation is usually extranodal. Primary CNS lymphomas (PCNSL) are high-grade lymphomas of B cell origin; Most common in individuals with immunodeficiencies, and may present in as much as 17 percent of pediatric patients[12] to 27 percent of adult patients with AIDS.[5]

In many cases the diagnosis of NHL may be the presenting illness of HIV infection, and thus fulfill the criteria for the diagnosis of AIDS at the outset. Also of note is the increased incidence of PCNSL. A significant proportion of the tumors have been found to have Epstein-Barr virus (EBV) present in the tumor tissue. Other infectious agents (human T cell leukemia virus type I, Hepatitis C, *Helicobactor pylori*) and environmental factors (pesticides, solvents, chemotherapy and radiation) have been implicated in the development of NHL, possibly due to uncontrolled B or T cell stimulation.[13]

Incidence/Prevalence: Pre-HAART and Post-HAART Era

Some studies have shown that there has been a decrease in the incidence of NHL in the post-HAART era. The number of cases of NHL diagnosed in patients with AIDS went from 1115 between 1980 and 1989 (Pre-HAART) to 560 between 1996 and 2002 (Post-HAART).[5] Chiappini et al showed that the number of cases of NHL decreased from 13 between 1985 and 1995 to 1 between 2000 and 2004, in their cohort of 1,190 perinatally infected patients.[14]

Treatment and Outcomes

In general, if diagnosed early, NHL is a treatable cancer. Often in patients with HIV/AIDS diagnosis may be delayed because symptoms of lymphoma overlap with those of HIV infection. Also, as mentioned above, NHL in HIV tends to present at a more advanced stage. Underlying immunosuppression often exaggerates common side effects of chemotherapy. Best prognosis is achieved with early diagnosis and ART with combination chemotherapy. The HIV treating physician and the oncologist working closely together to coordinate timely institution of HAART or continuation of HAART with joint awareness of the drug-drug interactions is necessary for optimal outcomes. In many instances, concomitant opportunistic infections complicate the clinical picture and affect prognosis. In general, these infections should be treated before the institution of HAART, however, the patient's clinical condition may not permit delays. In our experience, of the 9 patients with NHL and AIDS, only one patient survived greater than 10 years, post chemotherapy.[9] With HAART onboard, reports of aggressive high-dose chemotherapy with rituximab, coupled with autologous stem cell transplant rescue have been reported to lead to a long-term survival.[15]

Primary CNS Lymphoma (PCNSL)

Overview

Although PCNSL is not an AIDS-defining illness, it is seen almost exclusively in individuals with immunosuppression. PCNSL is typically classified as a B cell NHL that is confined to the CNS. Many studies have reported that it occurs at an increased risk in people infected with HIV. Linkage studies comparing the cancer incidence in the general population, with that in the HIV infected population have estimated the standardized incidence rate (SIR) of PCNSL as high as 250 per 100,000 person-years in adults.[3] Some pediatric studies have found the incidence of PCNSL to be as high as 25 percent of all cancer diagnoses.[7] In the HAART era, however, the rate has been shown to be decreasing, as PCNSL is thought to occur more frequently in individuals with prolonged or profound immunosuppression.[6]

Clinical Presentation

PCNSL is a focal mass lesion that usually presents with focal neurological signs, but more often presents as lethargy, confusion, or mental status changes. Contrast MRI shows a ring-enhancing lesion with surrounding

edema. Differential diagnoses include infectious etiologies such as toxoplasmosis, or cryptococcosis. Multiple lesions point more towards infectious causes. Unfortunately, these types of confounding infections may cause a delay in the initial diagnosis of PCNSL. The need to treat these underlying illnesses may delay the initiation of chemotherapy, thus decreasing the chance of remission. PET scan may also be a useful adjunct as these lesions are usually metabolically active. Most are histologically high-grade and virtually all patients with PCNSL test positive for EBV.[16] Mortality is generally high, as most children with PCNSL have numerous AIDS-defining illnesses at presentation.

Treatment and Outcomes

Studies in non-HIV infected patients have shown that long-term survival is only achieved in approximately 20 percent of patients.[17] Treatment modalities include methotrexate, methotrexate in combination with other drugs, radiotherapy or high-dose chemotherapy and stem-cell rescue. Therapeutic considerations are similar to those outlined for the treatment of NHL in the previous section. It has since been shown that it is possible to treat individuals simultaneously with HAART and chemotherapeutic agents. Systemic high-dose methotrexate produces the highest response-rate (80-90%) with 5-year survival of 60-65 percent.[18]

Kaposi's Sarcoma

Overview

In the early 1980's, the recognition of the increase in cases of an aggressive form of Kaposi sarcoma (KS), previously a rare and benign tumor, raised the awareness of the existence of the later-defined acquired immunodeficiency syndrome.[19] In adults with HIV, the risk of developing KS has been shown to have decreased since the widespread use of HAART, but still elevated, SIR (95% CI) 3640 (3300-3980).[5] It has also been shown that the effect of HAART on maintaining or elevating CD4 counts has also been shown to decrease the risk of KS.[3] The incidence of KS is much lower in the pediatric population. Studies are limited, but one case series estimates the incidence to be approximately 5 percent in children with HIV.[12]

KS is a low-grade vascular neoplasm, characterized by spindle cell formation and mononuclear cell infiltration. It is associated with concomitant infection with human herpes virus-8 (HHV-8) and tumor biopsies stain positive for HHV-8 nuclear antigen-1 protein. There are four known clinical subtypes: Classic, Iatrogenic, AIDS-associated and African/endemic-type. The classic form affects older men of Mediterranean or Eastern-European ancestry. Iatrogenic is linked to immunosuppression. AIDS-associated KS in the United States is most prevalent in men who have sex with men (MSM). The African/endemic type occurs in individuals living in equatorial Africa and is most likely to affect younger individuals.[20]

Clinical Presentation (Figs 2.12.1 to 2.12.7)

KS is characterized by lesions that range in color from pink/red to purple/brown to black in darker-skinned individuals. The skin is the usual site of initial presentation, but KS can occur anywhere.[21] Children are most likely to present without classic skin findings but instead may present with lymph nodes. Edema is a frequent complication and may be mediated by either involvement of dermal lymphocytic vessels or by cytokine production. If present in the oral cavity, KS most commonly presents as plaques and nodules on the hard or soft palate. Affected individuals may have difficulty with speech or eating and may also develop bleeding, pain, tooth loss, or airway obstruction. Gastrointestinal lesions may develop in the absence of cutaneous lesions. These lesions are often asymptomatic and are often found only at autopsy. If clinically significant, individuals may present with abdominal pain and signs of obstruction. The lung parenchyma, pleural surfaces and the bronchial tree may also be affected. This is most commonly seen in AIDS-related KS. Patients may present with shortness of breath, hemoptysis, or on a routine screening chest radiograph, hilar adenopathy and pleural effusion may be found incidentally.[21] In children KS may present as just generalized lymphadenopathy.[22]



Fig. 2.12.1: Eyelid lesions



Fig. 2.12.2: Lymphadenopathic KS



Fig. 2.12.3: Lymphadenopathic KS—no skin lesions



Fig. 2.12.4: Nodules and plaques



Fig. 2.12.5: Polypoid skin lesions



Fig. 2.12.6: Skin nodules



Fig. 2.12.7: Palatal lesion

Treatment and Outcomes

Complete remission may be achieved by HAART alone, through immune system reconstitution. Radiation, surgical excision, intralesional chemotherapy and systemic chemotherapy are all additional modalities that may be employed. The number or location of lesions, how symptomatic they are and the underlying overall health of patients should be considered when determining what type of intervention, if any, should be used.[23] With increasing numbers of perinatally infected children living to adulthood, and a significant number of these with AIDS due to a multidrug resistant virus (MDRV), this group is at particular risk for KS.

Cervical Cancer

In 1993, the Centers for Disease Control (CDC) added invasive cervical cancer to the list of AIDS-defining diseases. The link between human papilloma virus (HPV) infection and cervical cancer has been well studied. Numerous studies have reported that HIV infected individuals have a higher rate of anogenital HPV infections, and thus anogenital malignancies.[24] An increased prevalence of latent HPV infections associated with cervical intraepithelial neoplasia (CIN) has been noted in HIVpositive women.[25-27] As the perinatally-infected population ages this will become more of a concern as these children become sexually active adolescents and adults. We routinely offer HPV vaccination to pre-teens and teens with perinatal HIV infection at our center. It will become increasingly important, to ensure that widespread HPV vaccination and appropriate screening for cervical dysplasia/neoplasia occur in this population.

Non-AIDS-Defining Malignancies

Leiomyosarcomas

Overview

The incidence of soft tissue sarcomas has been estimated to be approximately 1.1 per 100,000 in children ages 0-19 years old in the United States. This does not distinguish the different subtypes.[28] In particular, leiomyosarcomas and also leiomyomas (benign smooth muscle tumors) have been noted with increasing incidence in pediatric patients with HIV. Overall numbers of cancers in pediatrics are low, and even lower in those infected with HIV. Some studies have estimated the incidence of leiomyosarcomas to be as high as 17 percent,[29] but most of these studies have very small sample sizes or are case reports. Leiomyosarcomas have a uniform, dense cellularity under light microscope. Fusiform cells are arranged in fascicles or bundles, and the nuclei are hyperchromatic, with a high mitotic rate. Muscle-specific stains are positive for actin and desmin. *In situ* hybridization demonstrates Epstein-Barr virus (EBV) in tumor cells, but not adjacent normal cells.[30]

Clinical Manifestations

Leiomyosarcomas most commonly present in the gastrointestinal tract, spleen, or the lungs. Depending on the location, they may present as a painless abdominal mass, or with vague abdominal pain. They are aggressive tumors that are difficult to treat, have poor prognosis and overall low survival rates. Treatment depends on location and type and appears to be better in children.

Hodgkin's Disease

Overview

The incidence of Hodgkin's disease (HD) appears to be increased in adults with HIV infection.[5,31,32] Some studies suggest that the standardized incidence rate (SIR) of HD may be as high as 13.6 per 477,368 person-years, in individuals on HAART[5] HD is not as prevalent in children infected with HIV, as in the adult population. Nonetheless, this clinical entity will become more relevant as the pediatric HIV population ages.

Clinical Presentation

HD is distinguished by the presence of abnormal B lymphocytes, the Reed-Sternberg cells. The four subtypes are: Nodular sclerosing, mixed-cellularity, lymphocyte-rich and lymphocyte-depleted. Staging is based on nodal involvement, subtype and the absence or presence of systemic or B symptoms, i.e. fever, night sweats or weight loss. Patients with HIV typically present with advanced stage disease that is extranodal, and more often than not accompanied by B symptoms. Mixed-cellularity and lymphocyte-depleted are the most predominant subtypes. EBV infection may also play a role, as most of the HIV related lymphomas are EBV-positive.[31]

Prognosis Pre/Post/HAART Era

As mentioned above, a slight increase in the incidence of HD has been found, even in the era of antiretroviral therapy. It has been postulated that this increase might be due to immune reconstitution.[3] Survival rate in the general population approaches 90 percent, if detected in the earlier stages. Prior to HAART, HIV infected patients with lymphoma had limited survival of 1-2 years. Concurrent use of HAART and chemotherapy with/without radiation therapy has improved the response rate and increased survival in this population. Of the two patients with HIV and HD followed by our center, one had stage 2 HD with HIV disease class A-1, and the other had stage 4S, class C-3. The first did very well with standard chemotherapy and went on to early adulthood

and had a noninfected baby ten years later. She is still alive at the time of this publication. The second had a long history of nonadherence to HAART and had a multidrug resistant HIV infection. He died of AIDS-related complications during induction therapy soon after diagnosis of HD.

Psychosocial Aspects

Physicians caring for children with HIV infection already have the task of working with the family and the child to help them deal with the difficulties of the stigma associated with HIV, and related issues of disclosure of the diagnosis to the child as the child grows. When an additional immediate life-threatening diagnosis of cancer is added, it is often emotionally devastating. Team members who care for these patients often have long-standing relationships themselves with the patients and the emotional grief and pressure felt by them should not be ignored. A multidisciplinary approach, including mental health support systems, is critical to provide adequate support to patients and families.

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(*Photo courtesy:* Dr Rajendra Thejpal, Principal Specialist, Pediatric Hematologist, University of Kwazulu Natal/Inkosi Albert Luthuli Hospital, Department of Health, Kwazulu Natal, Durban, South Africa).

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2.13

Opportunistic Infections in HIV Infected Children

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The Human body is constantly being exposed to micro-organisms from the environment and infectious individuals. These microorganisms which include bacteria, viruses, fungi and parasites are prevented from invading the human body by an intact innate and adaptive immune response. Therefore an individual with an intact immune response is able to prevent invasion and infection from these microorganisms.

HIV/AIDS is the prototype of a secondary immunodeficiency syndrome resulting in predominantly a cellular immunodeficiency but also results in defects of both the humoral and innate immunity resulting in an increased susceptibility to many infectious diseases. Patients with clinical AIDS present with a higher incidence of common infectious disease but also an increased incidence of opportunistic infections (infections that under normal conditions do not cause clinical disease). The prevalence of specific infectious diseases is dependant on the incidence of the microorganism within the community. Opportunistic infection (OI) refers to an infection by a microorganism that normally does not cause disease but becomes pathogenic when the body's immune system is impaired. HIV related opportunistic infections can be caused by a wide variety of pathogens which are found in the environment. Children can acquire an opportunistic infection either vertically from the mother, or horizontally from the environment, from food and water or from interaction with animals.[1] It is possible that HIV infected women are more likely to transmit opportunistic pathogens to their infants. Generally, an OI in a child is a primary infection (as opposed to an adult where it is usually a reactivation).

The risk of developing an opportunistic infection depends on the state of the immune system. In children with HIV, the CD4 count is used as a measure of the functioning of the immune system. Whilst it is well-known that the risk of an opportunistic infection increases as the CD4 count declines, it is important to note that, in children, OIs can occur even with a relatively normal CD4 count (Fig. 2.13.1). Certain diseases are likely to occur at different levels of CD4 counts. For example, tuberculosis and oral thrush can occur even when the immune system is relatively healthy, while other infections usually do not appear until late in the course of HIV disease.

The natural history of OIs among children might differ from that among HIV infected adults.[1]

Over the past few years, much has occurred to change the landscape of OIs in children. These changes include the following:

- The effect of earlier initiation of HAART, especially with wider access to HAART and improved treatment guidelines, which impacts on the number and severity of OIs[2]
- The effect of initiation of HAART during an OI, although the question of the optimal timing of initiation of HAART after starting treatment for an OI has still not been resolved[2, 3]
- The risk of developing IRIS after initiation of antiretroviral therapy
- Revised criteria for primary prevention
- Revision of criteria for secondary prevention
- New diagnostic tests, leading to an improvement in the diagnosis of OIs

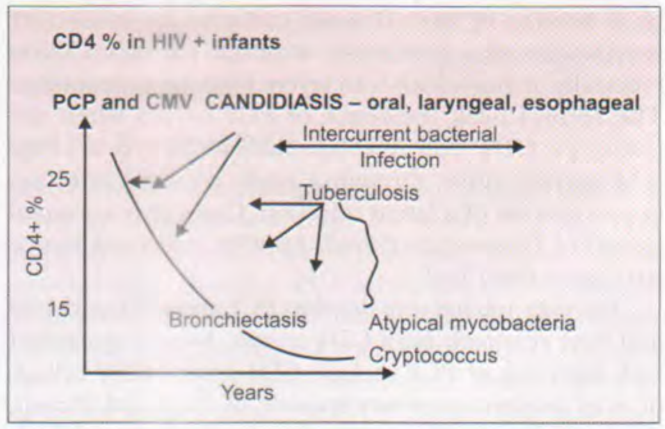


Fig. 2.13.1: Relationship between CD4 count and onset of opportunistic infections (with permission, M Cotton)

- New vaccines becoming available preventing specific OIs, e.g. HPV, Pneumococcal
- The development of new drugs for the treatment of OIs, and the development of pediatric formulations
- Drug-drug interactions, e.g. between ARTs and drugs used in the treatment of an OI.

Fungal Infections

Pneumocystis Jirovecii Infection

Microbiology

The taxonomy and classification of this ubiquitous organism has changed over the past few years. Initially thought to be a protozoa, it has now been reclassified as an atypical fungus. However pneumocystis infections typically will respond to antiprotozoan drugs and not to antifungal drugs. Pneumocystis fails to grow on standard culture media and therefore can not be isolated by culture in the routine laboratory.

The taxonomy of the organism has also changed to *Pneumocystis jirovecii* being the species infecting humans only. The widely used acronym of PCP has been retained and refers specifically to Pneumocystis pneumonia.

Epidemiology

Pneumocystis has a worldwide distribution and is spread by the airborne route. Although the environmental reservoir is unknown, pneumocystis has been isolated from water, air samples surrounding infected individuals and is probably extensively distributed in the environment. Healthy children are exposed to *Pneumocystis jirovecii* early in infancy, with up to two thirds of all children developing antibodies to *Pneumocystis jirovecii* by 2-4 years of age; this infection in immunocompetent children is usually asymptomatic.[4] This initial infection accounts for the high incidence of PCP in immunocompromised infants between 6 weeks to 6 months of age. Disease can also be caused by reactivation of a previously acquired latent infection especially in individuals with severe immune suppression. The second peak incidence of PCP occurs when the patient's CD4 count drops below 200 cell/μl or <14 percent either through a newly acquired infection or reactivation of a latent infection. Cases of nosocomial spread of *Pneumocystis jirovecii* from an infectious source have been described.

Typically infants who develop PCP are well nourished and have relatively high CD4 counts. Factors associated with high risk of PCP include CD4 count <200 cell/μL or <14 percent, previous episode of PCP, oral thrush, recurrent bacterial pneumonia, weight loss and high plasma HIV viral load.

The benefits of HAART on mortality and morbidity have been clearly demonstrated among adults receiving specialized HIV care in developed countries.[5] Further, many studies have documented the decrease in the hospital admission rates and mortality of patients with PCP who are concurrently on HAART.[2] These findings correlate with an increased CD4 count and a decrease in HIV-1 RNA viral load, due to the use of HAART. Morris et al described a cohort of HIV infected adults with PCP pneumonia admitted to ICU, and described a decrease in mortality associated with severe PCP in patients on HAART.[6,7] The mortality of patients not receiving HAART was 63 percent versus 25 percent in the group receiving HAART. The effect of HAART on mortality was strongest if HAART was initiated before admission (16.7% mortality) and weakest if HAART was initiated during the admission (33.3% mortality).[8,9]

Clinical Presentation

The most common presentation is pulmonary involvement. The clinical presentation of PCP can vary; young infants typically present with an abrupt onset of respiratory distress while older children with low CD4 counts present with the insidious onset of progressive hypoxia similar to adult disease.

Infants present with acute onset of severe respiratory distress and fever in a child who is HIV exposed but typically having a normal weight and is asymptomatic or mildly symptomatic (WHO stage 1 or 2). On examination of the chest the patient typically is in severe respiratory distress with minimal additional sounds, out of keeping with the degree of respiratory distress. The arterial blood gas usually reveals a type 1 hypoxic respiratory failure with a low PaO_2 and normal $PaCO_2$. Uncommon presentations include lethargy, weight loss and the absence of pyrexia.

Extrapulmonary involvement is rare and can occur with or without pulmonary involvement. Case reports of extrapulmonary pneumocystis include involvement of the ear, eye, thyroid gland, GI tract, spleen, adrenal glands, bone marrow, heart, kidney, lymph nodes, meninges, cerebral cortex and muscle. The clinical presentation will vary depending on the organ involved and include sudden hearing loss, visual impairment, thyroiditis and ascites or colitis. The incidence of extrapulmonary pneumocystis in children is unknown but in adults it is reported as 0.06-2.5 percent of all pneumocystis infections.

Laboratory Diagnosis

The diagnosis of PCP is made on the basis of a combination of suggestive clinical scenario and supportive laboratory evidence (Table 2.13.1).

Table 2.13.1: Methods of detection of PCP

Technique	Sensitivity/ Specificity	Method
Nasopharyngeal aspirate		Catheter is inserted into the nasopharynx and 3-5 ml of normal saline is instilled and immediately aspirated
Induced sputum	50/90%	Patient nebulized with hypertonic saline +/- a bronchodilator to induce a cough. Physiotherapy administered and sputum aspirated.
Broncho-alveolar lavage (BAL) with or without Bronchoscopy	90/99%	Aspiration of fluid directly from the bronchus either with direct visualization using a bronchoscopy or blindly
Transbronchial biopsy	95/100%	Lung biopsy obtained via a bronchoscope
Open lung biopsy	95/100%	Requires a thoracotomy. Seldom performed now

The typical clinical scenario is an HIV exposed infant (HIV positive or HIV status unknown) presenting between the ages of 6 weeks and 1 year with acute onset of severe respiratory distress and fever.

Arterial blood gas reveals profound hypoxia with a low PaO_2 between 34 to 73 mm Hg.

The serum Lactate Dehydrogenase (LDH) is often raised in PCP but is not specific for pneumocystis infection. The level of LDH can be used as a prognostic marker of severity of the infection.[10]

There is no distinctive feature of PCP on chest X-ray. The X-ray changes may vary from a normal chest X-ray to lobal collapse with air bronchograms. The classically described chest X-ray picture of PCP is of hyperinflation with bilateral pulmonary infiltrates giving the lung a "ground glass" appearance. Pneumatoceles, air bronchograms and alveolar infiltrates may be present.

Pneumocystis serology: Detection of antibodies to pneumocystis has limited use in clinical practice.

The definitive diagnosis of PCP is by identification of the organism in clinical specimens. Because PCP cannot be cultured in the routine microbiology laboratory, pneumocystis can be identified by histology or special staining techniques of clinical specimens. Alternative methods of identification now in current use include Fluorescent Monoclonal Pneumocystis Antibody staining and PCR techniques.

Appropriate specimens are vital in order to improve the yield and identifying the organism. The specimens need to contain respiratory secretions from the distal portion of the respiratory tree to have a high sensitivity.

Specimens include

Commercially available kits containing monoclonal antibodies against both cysts and trophozoites improve the sensitivity of staining techniques but are more expensive.

The use of nucleic acid amplification to detect pneumocystis is also available. But the expense of the test may limit its use especially in the developing world.

Prevention

The incidence of PCP in many developed countries has decreased significantly with the introduction of Highly Active Antiretroviral Therapy (HAART) and effective PMTCT programs reducing the number of HIV infected infants. In infants where PCP can occur even with a high CD4 count, the current WHO guideline for the initiation of HAART in all HIV infected infants will result in a decrease in the incidence of PCP provided that HAART is initiated early.

Primary drug prophylaxis is indicated in all patients with a CD4 count below 200 cell/μl and in all HIV exposed infants. In HIV exposed infants PCP prophylaxis is commenced from 4-6 weeks of age (Table 2.13.2).

Alternative drugs in patients with cotrimoxazole intolerance include Dapsone, Atovaquone, or Dapsone +Pyrimethamine+Leucovorin. The recommended dose of Dapsone is 2 mg/kg/day or 4 mg/kg/week with a maximum daily dose of 100 mg.

Patients who develop mild adverse reactions or non-life threatening adverse events associated with the use of cotrimoxazole should be re-challenged with cotrimoxazole starting at a lower dose and with an increasing dose up to standard dosage or started with cotrimoxazole at a reduced frequency (e.g. alternate day regimen).

Secondary prophylaxis for PCP should be commenced in all patients who have a previous diagnosis of PCP.

Management

The management of a patient with PCP includes both specific therapy for PCP and nonspecific supportive management.

Specific Therapy (Table 2.13.3)

Cotrimoxazole is the drug of choice for patients with PCP either as intravenous therapy for severe PCP and oral outpatient therapy for mild to moderate disease. Even in patients who develop PCP while on cotrimoxazole prophylaxis, cotrimoxazole remains the drug of choice. The duration of therapy is for a minimum of 21 days at a dose of 15-20 mg/kg/day Trimethoprim and 75-100 mg/kg/day of sulfamethoxazole IVI 6 hourly. The oral dose of 20 mg/kg/day Trimethoprim and 100 mg/kg/days of sulfamethoxazole can be used to complete the 21 day course in mild-moderate disease.

Table 2.13.2: PCP prophylaxis

Indications for PCP prophylaxis	When to start	When to stop
All HIV exposed newborns	Start from 4-6 weeks after birth	Stop when PCR negative ≥6 weeks after full weaning AND infant is clinically HIV negative.
All HIV exposed Exclusive formula feeding children (EFF)	Start from 4-6 weeks after birth	Stop when PCR negative AND infant is clinically HIV negative AND EFF is expected to continue
All HIV exposed breastfeeding children	Start from 4-6 weeks after birth	Stop when PCR negative ≥6 weeks after full weaning AND infant is clinically HIV negative
HIV infected infants <12 months old	Start from 4-6 weeks after birth or as soon as possible after HIV diagnosis even if on ART. Note: all HIV positive infants <1 year should be started on ART regardless of clinical stage or CD4 count or percentage	All infants <12 months should remain on prophylaxis
For HIV infected children 1-5 years with or without ART	All symptomatic children (WHO clinical stage 2,3 or 4) or CD4 <15% or <500 cells/mm^3	Stop once ART-associated immune reconstitution has occurred for ≥6 months, i.e. CD4 percentage ≥15% or CD4 count ≥500 cells/mm^3 on ≥2 occasions, 3-6 months apart
HIV infected children ≥6 years of age with or without ART	Start if CD4 count < 200 cells/mm^3 or<15% OR WHO clinical stage 3 or 4 disease (including tuberculosis)	Stop once ART-associated immune reconstitution has occurred for ≥6 months in children over 1 year of age: CD4 ≥15% or ≥200 cells/mm^3 on ≥2 occasions, 3-6 months apart
Any HIV infected child with high risk for bacterial infections, e.g. severe malnutrition, on oncological drugs or corticosteroids or at risk of malaria	Start cotrimoxazole prophylaxis even with ART immune-reconstitution.	Do not stop until risk has been eliminated and all CD4 cell percentage or CD4 cell count criteria listed above have been met
HIV infected child with previous PCP infection	Start as soon as first PCP episode has been treated	Stop at age 5 years

Adjunctive corticosteroids are indicated for moderate-severe disease (Defined by a PaO_2 <70 percent at room air or an a-A gradient >35 mm Hg). Corticosteroids should be initiated within 72 hours of commencement of cotrimoxazole therapy for maximum benefit. Corticosteroids should be used with caution when polymicrobial infections are suspected.

Response to therapy should be seen within 4 to 8 days after initiation of appropriate therapy. Failure to respond to therapy may be due to infections with other common opportunistic infections including cytomegalovirus (CMV), mycobacterium tuberculosis, Mycobacterium other than tuberculosis (MOTTS) or treatment failure due to drug-resistance.

Alternative treatment regimens include intravenous pentamidine or clindamycin—primaquine for moderate-severe disease and Dapsone—trimethoprim or atovaquone for mild-moderate disease.

Nonspecific Therapy

Maintain oxygenation with a target oxygen concentration of >70 mm Hg preferably with the use of supplemental oxygen either via a rebreather mask or continuous positive airway pressure ventilation (CPAP). Patients who are unable to maintain oxygenation with supplemental oxygenation or with a PaO_2 <60 mm Hg are candidates for mechanical ventilation. The rational use of mechanical ventilation in resource poor countries is an ethical dilemma for many clinicians, especially with the poor outcomes postventilation (prognosis).

Maintaining adequate hydration and nutrition during the acute episode especially in children who are severely distressed and are unable to feed is imperative.

Initiation of antiretroviral therapy in patients with PCP should be considered. Some studies have suggested the benefit of early initiation of HAART in patients with PCP, however randomized controlled trials are lacking.

Table 2.13.3: PCP prophylaxis

The drug of choice for prophylaxis is cotrimoxazole at the following doses

Age or weight of child	Dose	Suspension (200 mg SMX/ 40 mg TMP/5 mL)	Single strength tablet (400 mg SMX/ 80 mg TMP)	Double strength tablet (800 mg SMX/ 160 mg TMP)
<6 months or <5 kg	100 mg SMX / 20 mg TMP	2.5 mL	¼ tablet	–
6 months -5 yrs or 5-15 kg	200 mg SMX / 40 mg TMP	5 mL	½ tablet	–
6-14 years or 15-30 kg	400 mg SMX / 80 mg TMP	10 mL	1 tablet	½ tablet
>14 years or >30 kg	800 mg SMX / 160 mg TMP	-	2 tablets	1 tablet

Potential problems with the cotreatment with anti-PCP treatment and HAART include overlapping toxicities and the development of PCP IRIS.

The mortality of patients with PCP pneumonia in developed countries varies from 60 percent in the late 1980 (Pre HAART era) to 10 percent in recent studies. The benefits of HAART on the mortality and morbidity have been clearly demonstrated among adults receiving specialized HIV care in developed countries. Concurrent prescription of Highly Active Antiretroviral Therapy (HAART) was associated with surviving the early period in PCP in adult patients with AIDS in the United States. While the initiation of HAART has been shown to reduce the mortality associated with PCP pneumonia in adult patients, in developing countries the burden of PCP pneumonia is in infants predominately between the age of 8 weeks and 6 months. These infants have often not been diagnosed as being HIV positive, may not have received PCP prophylaxis and have not been started on HAART.

Candidiasis

Candida albicans is the commonest fungal infection among HIV infected children. Candida can infect a child's mouth, throat, or skin (particularly the perineum). Candida can also spread and cause infection in the brain, heart, joints and eyes. Disseminated candidiasis occurs in neonates, those with indwelling catheters, patients who are critically ill, and in those who have been treated with long-term systemic antibiotics.

Clinical Manifestations

Signs and symptoms

The oropharynx is usually affected, with the presence of white, nonadherent plaques on the buccal mucosa and tongue. The child may present with refusal of feeds or drooling. The infection often includes involvement of the esophagus. Esophageal candidiasis is an AIDS-defining illness. Oropharyngeal candidiasis remains a problem despite HAART. Esophageal candidiasis in a child on HAART may be an indication of treatment failure. Esophageal candidiasis may occur in the absence of oral candidiasis.

Suspect esophageal candidiasis, if a child with oral candidiasis:

- refuses feeds
- has swallowing difficulty
- drools or
- has a hoarse voice or stridor.

Diagnosis

Diagnosis in the oropharynx can be made based on the clinical appearance. Candida esophagitis can also initially be diagnosed clinically.

Treatment

Treatment can be local or systemic. Local treatment is applied where the infection is found.

Outpatient management

- Give nystatin drops 1ml 4 hourly ±30 minutes after feed for 7 days. If the child is breastfed, check for breast thrush and treat the mother accordingly. If the response is poor add miconazole oral gel and apply 4 to 6 hourly to oral mucosa for 7 to 14 days
- Relieve pain with paracetamol. Topical analgaesia may be of benefit—Choline salicylate gel or benzymadine mouthwash
- Refractory oral candidiasis, or if esophageal candidiasis is suspected:

  Treat with fluconazole 3 mg/kg/day for 21 days.

Systemic treatment is needed if local treatment does not work, or if the infection has spread into the throat (esophagitis) or other parts of the body.

A child with severe oral thrush may not be able to feed/eat. In this case, attention must be paid to nutrition. Avoid foods that are spicy, pungent, hot in temperature, and acidic. Encourage the child to have cold liquids, very soft bland food, and use of straws if necessary.

Esophageal Candidiasis

Treat with fluconazole 3 mg/kg/day for 21 days intravenous, changing to oral fluconazole if tolerating feeds. It is important to provide pain relief.

Prevention

Preventing candidiasis is almost impossible. Primary and secondary prophylaxis are not recommended, as the infection is treatable.[11]

Cryptococcal Disease

Cryptococcus is a fungus which is commonly found in the soil. Infection occurs by dust inhalation or through bird droppings. There is no human transmission, but placental transmission can occur rarely. Meningitis is the most common form of the disease. It is important to maintain a high index of suspicion in an HIV infected person with fever and headache.

Clinical Manifestations

Cryptococcal infection can occur in the bones, joints, skin and CNS. Meningitis is the most common illness caused by Cryptococcus.[12] The risk of cryptococcal infection is highest when the CD4 counts are very low. The signs of meningitis include fever, a stiff neck, headache, and vomiting. Cryptococcal infection can cause pneumonia in immunocompromised children and is the commonest cause of a fungal pneumonia.

Diagnosis

Diagnosis is made on lumbar puncture and by finding the antigen on blood testing. However, there is no "typical" CSF picture with cryptococcal infection. The opening pressure is usually elevated. CSF must be sent to the lab for staining and for the presence of antigens. The India ink stain on wet mount preparation is positive on direct examination of the CSF in over 80 percent of patients with cryptococcal meningitis. Cryptococcal antigen can be detected in CSF, serum, or bronchoalveolar lavage fluid by the latex agglutination test.[13]

Lesions from the skin, bones and joints can be aspirated or biopsied and cultured.

Treatment

- Severe
  - Amphotericin B (0.5-1.0 mg/kg), IV × 2 weeks, thereafter fluconazole (12-15mg/kg per day, maximum 400 mg) to complete 8 to 10 week course.
- Followed by fluconazole only × 6 weeks 6 mg/kg
- For raised intracranial pressure:
  - serial lumbar punctures if older child
  - external shunt
  - diuretics in younger child

  All children with suspected Cryptococcal meningitis need to be treated initially as inpatients;
- Disseminated cryptococcal disease: Treat as for meningitis.

Prevention

Primary prophylaxis is not recommended.

Secondary prophylaxis:

- organism remains for life
- lifelong secondary prophylaxis with fluconazole dose 6 mg/kg/day

After therapy, secondary prophylaxis should be continued indefinitely. Fluconazole (6-10 mg/kg per day) may be effective. For adolescents receiving antiretroviral therapy maintenance fluconazole may be stopped if immune reconstitution occurs-CD4 count increases to between 100-200 cells. There are no data available to confirm that stopping maintenance therapy in children is safe.

Viral Infections

Viral Hepatitis

There are many viruses that can cause hepatitis. Those that are known to date include hepatitis A, B, C, D, E, and G viruses. Most cases of hepatitis are caused by hepatitis A, B, or C.

Hepatitis B

Hepatitis B virus is a hepadnavirus, with a circular genome composed of partially double-stranded DNA. Although replication takes place in the liver, the virus spreads to the blood where virus-specific proteins and their corresponding antibodies are found in infected people.

Transmission

Hep B can be acquired through mother to child transmission, through sexual contact, or through contact with infected blood.

Clinical Manifestations

Hepatitis B infection can be acute or chronic. Most acute HBV infections in children are asymptomatic. Prodromal symptoms of lethargy, malaise, fatigue, nausea and anorexia can occur. Jaundice and right upper quadrant pain follow and, less commonly, hepatomegaly and splenomegaly.

Chronic hepatitis B infection is defined as persistence of hepatitis B surface antigen (HbsAg) for >6 months. Most children with chronic HBV infection are asymptomatic.

About 25 percent of infants and children with chronic HBV will eventually develop cirrhosis or hepatocellular carcinoma.[14,15]

Acute infection with hepatitis B virus is associated with acute viral hepatitis—an illness that begins with general ill-health, loss of appetite, nausea, vomiting, body aches, mild fever, dark urine, and then progresses to development of jaundice. The illness lasts for a few weeks and then gradually improves in most affected people. A few patients may have more severe liver disease and may die as a result of it. Chronic infection with hepatitis B virus may be either asymptomatic or may be associated with chronic inflammation of the liver (chronic hepatitis) leading to cirrhosis over a period of several years.

Diagnosis

The tests used for detection of hepatitis B virus infection involve serum or blood tests that detect either viral antigens or antibodies produced by the host.

The hepatitis B surface antigen (HBsAg) is most frequently used to screen for the presence of this infection. Shortly after the appearance of the HBsAg, the hepatitis B e antigen (HBeAg) will appear. During the natural course of an infection, the HBeAg may be cleared, and antibodies to the 'e' antigen (anti-HBe) will arise immediately afterwards. If the host is able to clear the infection, eventually the HBsAg will become undetectable and will be followed by IgG antibodies to the hepatitis B surface antigen and core antigen (anti-HBs and anti HBc IgG).

Individuals who remain HBsAg positive for at least six months are considered to be hepatitis B carriers. PCR tests have been developed to detect and measure the amount of HBV DNA in clinical specimens. These tests are used to assess a person's infection status and to monitor treatment.

Treatment

Antiviral regimens are not recommended for children <2 years of age, and for children with normal transaminases.

Indications for treatment:

- Ongoing viral replication
- Evidence of chronic hepatitis on liver biopsy.[15]

Treatment of Hep B infection in children is an evolving process; therefore consultation is important.

There are several possible scenarios to consider:

- HAART not required:
  - Interferon-alpha would be drug of choice
  - Consider using Adefovir in older children
  - Avoid drugs used in HAART, e.g. lamivudine
- HAART required, but not treatment for Hep B:
  - Use ART agents without anti-Hep B activity
  - Therefore avoid lamivudine, tenofovir
- Treatment for both HIV and Hep B is indicated:
  - Use a regimen containing lamivudine
  - Tenofovir can be used in older children
- Treatment for both HIV and Hep B is indicated and child already on HAART:
  - Consider the possibility of lamivudine resistance
  - Addition of Inteferon
  - Use Tenofovir or Adefovir in older children

Minimum duration of Rx is 6 months, with close monitoring of transaminases. Note that elevated enzymes may be due to IRIS.

Hepatitis B Viral Load can be used to monitor response to treatment.

Primary prevention

Prevention of exposure by testing of all pregnant women, and vaccinating against Hep B during pregnancy

Preventing first episode

If a newborn has been exposed *in utero*, the infant must receive the Hep B vaccine as well as immunoglobulin. Ensure that all infants receive Hep B vaccine as per country schedule.

Refer to the chapter on Hepatitis B and HIV Co-infection in Children for more details.

Hepatitis C

Little is known about Hepatitis C infection in children, and about its prevalence in developing countries. Most of the available information is based on studies in adults in developed countries.

Transmission

Hepatitis C is usually spread by direct contact with blood, by blood transfusion, and by mother to child transmission.[16] The rate of maternal—infant transmission of HCV is approximately 5 percent.[9] This risk is 3-4 times higher if the mother has both HIV and HCV.[16, 17]

Clinical manifestations

Children with perinatal HCV infection appear to have a more benign clinical course than do adults.[7] Most HCV-infected children are asymptomatic with minor abnormalities,[18] such as hepatomegaly, or mild nonspecific symptoms, such as fatigue, myalgias, and poor weight gain. HIV worsens hepatitis C. Most chronic hepatitis C in children is because of mother-to-infant transmission. Chronic Hep C infection can lead to cirrhosis of the liver.[19]

Diagnosis

The diagnosis of Hep C infection is made by antibody test or by viral load testing. Infants born to women infected with HCV should be tested using antibody to HCV at 12 to 18 months of age.[10] Before 9 to 15 months of age, the HCV RNA test is used to identify HCV infection. HCV RNA levels may take time to reach the threshold for PCR detection in many neonates, levels of HCV RNA may fluctuate and accelerated spontaneous clearance may also occur.

Treatment

Hepatitis C can be treated using a combination of 2 drugs, pegylated Interferon and Ribavirin.[20] Drugs are given for between 3 to 12 months.

Prevention

There is currently no vaccine available. All blood and blood products should be screened prior to transfusion. Planned delivery by Cesarean section (C-section) reduces the risk of mother-to-child HCV transmission among HIV positive mothers. HCV treatment is not recommended during pregnancy, as Ribavirin can be teratogenic.

Hepatitis C and HIV coinfection

HIV increases liver damage from Hepatitis C. Coinfected people are more likely to have liver problems from anti-HIV drugs. The lower the CD4 count, the higher the risk of liver damage. Coinfected people usually have a higher Hepatitis C viral load, which means that treatment may be less likely to work.

Some HIV drugs must be avoided during HCV treatment.[21] Do not use Didanosine (ddI) with Ribavirin. Avoid Zidovudine (AZT) during HCV treatment because it increases the risk for anemia.[21]

Refer to the chapter on Hepatitis C and HIV Co-infection in Children for more details.

Cytomegalovirus

Virology

Cytomegalovirus (CMV) is a large double stranded DNA virus that belongs to the Herpes family of viruses. Like other herpes viruses, primary CMV infection usually occurs early in life which may or may not be symptomatic. Thereafter CMV can remain latent in lymphocytes where the virus is quiescent and can reactivate when immune function is impaired. In immune-compromised patients the primary infection can be more severe and reactivation can be more frequent and severe.

Transmission of CMV can be vertical or horizontal. Vertical transmission occurs either *in-utero* or peri-partum (resulting in a clinical syndrome of congenital CMV) or post partum from CMV infected breast milk. Horizontal transmission occurs from exposure to infected blood, saliva, tears, urine, stool or genital secretions. Most infections occur during early infancy from spread within the family from infected saliva or urine. A second peak in incidence occurs in adolescence through sexual transmission.

Coinfection with HIV and CMV results in infection of lymphocytes, and results in a complex interplay between the two infections.[22] CMV infected cells up-regulate HIV expression and also increase the susceptibility of lymphocytes to infection with HIV. Therefore coinfection with HIV and CMV causes more rapid disease progression to AIDS because lymphocytes are more likely to be infected with HIV and have higher viral relication. Coinfection also results in increased CMV replication particularly when the CD4 count is below 50 cells /cu mm.

Epidemiology

In developing countries majority of infections occur during early infancy and most individuals eventually become infected during their lifespan.

Congenital CMV infection (intra-uterine infection) occurs due to mother-child transmission of CMV during an acute infection or reactivation of CMV during pregnancy. An acute CMV infection during pregnancy is more likely to produce the clinical syndrome of congenital CMV, which includes mental retardation, sensori-neural deafness and chorioretinitis.[23] Perinatal CMV occurs due to the exposure of the neonate to CMV either during the delivery or from infected breast milk in 25 to 60 percent of exposed infants.

Opportunistic CMV infections can be the result of reactivation of a latent infection or reinfection by a new stain of CMV in a previously infected individual. Before the advent of HAART almost 30 percent of all patients with AIDS developed CMV retinitis at some stage before death. Risk factors include severe immunosuppression (especially CD4 count <50 cells/ul), high HIV plasma viral load (Viral load >100000 copies/ml) and previous opportunistic infections.[24,25] With the use of HAART particularly with initiation at higher CD4 cut-off values, the incidence of CMV OIs has decreased by 75 to 80 percent. Patients with established CMV retinitis also benefit from HAART with a lower rate of recurrence of disease.

Clinical Presentation

CMV infections occur in 8 to 10 percent of children with WHO Stage 4 disease, with a quarter of these infections resulting in CMV retinitis and the remainder of infections causing infections in the lung, liver, colon and brain.

CMV Retinitis: Is the most common clinical manifestation in adults and children. The initial presentation is usually unilateral; however if untreated, systemic dissemination and bilateral eye involvement is an eventual consequence in most patients. CMV retinitis is a largely under-diagnosed condition in young children, therefore all children with suspected CMV infection should be screened for CMV retinitis. Older children usually will complain of loss of vision or the presence of floaters in the visual fields.

On ophthalmologic examination the characteristic lesions are fluffy yellow-white retinal lesions, with or without intraretinal hemorrhages. Peripheral lesions may have a more granular appearance. Progression of the retinitis occurs intermittently with a brushfire pattern, with a central area of scar formation and an advancing granular white leading edge.

CMV Colitis: The incidence in children is unknown, but CMV colitis is a common cause of lower gastrointestinal bleeds and perforation in children with AIDS. Clinical presentation includes fever, abdominal pain, persistent diarrhea, weight loss and anorexia. Presentation with a sudden onset of severe abdominal pain usually indicates perforation or hemorrhage requiring surgical intervention.

CMV Gastrointestinal Disease: CMV may also cause an esophagitis or chronic oral or esophageal ulceration. Symptoms include poor feeding, anorexia, pain on swallowing, fever and substernal pain. CMV can also cause gastritis and rarely a pancreatitis.

CMV Hepatitis: CMV hepatitis is common and typically causes a mild hepatitis. Patients are usually asymptomatic

with elevated AST/ALT and ALP and a normal bilirubin. On liver biopsy typical owl's eye inclusions are seen.

CMV Pneumonitis: The identification of CMV from pulmonary aspirates or tissue may indicate active CMV pneumonitis or an innocent by-standing latent infection in lymphocytes. The reported incidence of CMV pneumonitis in adults is low and is associated with a CD4 count 50 cells/mm^3 and disseminated disease. Clinical presentation includes a nonproductive cough with gradually worsening respiratory distress.

CMV Neurological Disease: CMV can cause a ventriculo-encephalitis, CMV-related encephalopathy and an ascending polyradiculopathy. CMV ventriculoencephalopathy presents with an acute onset of focal neurological signs and cranial nerve palsies with rapid progression to death. Neuroimaging demonstrates periventricular enhancement. Ascending polyradiculopathy presents similar to Guillian-Barre syndrome with urinary retention and ascending worsening muscle weakness progressing over weeks.

Laboratory Diagnosis

The major diagnostic dilemma is differentiating between CMV infection and CMV disease, especially in developing countries where CMV is a ubiquitous childhood infection that is largely asymptomatic. Detection of CMV antibodies or antigen indicates that the patient is or has been infected with CMV but does not necessarily indicate that it is causing disease, proving that CMV disease requires evidence of CMV end-organ damage and detection of CMV from that site. In HIV infected individuals CMV viral shedding may be prolonged therefore detection of CMV from urine and throat swabs proves infection and not disease.

Serology: Outside of the neonatal period CMV serology is of limited use especially in developing countries where majority of the population will seroconvert especially during childhood. Detection of CMV IgG indicates that the individual has been infected with CMV in the past, however, a negative IgG makes CMV disease highly unlikely. In the neonatal period detection of CMV IgM or CMV IgG indicates perinatal transmission of CMV. Combination of clinical features of congenital CMV and positive serology is diagnostic for Congenital CMV disease.

CMV Antigenaemia: Detection of the viral matrix protein pp65 on infected neutrophils indicates CMV infection which may be an acute or a latent infection. The drawback is that samples must be processed within 6 hours.

Viral Culture: Culture of CMV on laboratory cellular lines from sites associated with disease can be used in diagnosis of CMV disease. Traditional viral culture of CMV requires 1 to 3 weeks while newer shell vial culture techniques can detect the virus within 24 to 48 hours. Culture of CMV from urine and throat swab specimens indicates viral shedding and may not indicate CMV disease. Cultures from CSF, vitreous humor, bronchial aspirates and biopsy samples usually indicate CMV disease at that site. CMV can be cultured in only two thirds of patients with proven CMV infections.

CMV DNA PCR: Detection of CMV by polymerase chain reaction has a higher sensitivity than CMV culture for detection of CMV and a high CMV viral load (>100 – 1000 copies/ul) predicts end-organ damage. CMV DNA PCR can be performed on blood, urine, vitreous, bronchial aspirates and biopsy specimens.

Histology: Demonstration of the characteristic histopathological feature of CMV infection provides evidence of cellular infection at the site of the biopsy. CMV infection typically causes intranuclear and intracellular inclusion bodies resulting in an "owl's eye" appearance.

Prevention

The early initiation of HAART is the most effective method of preventing CMV end organ disease. The use of prophylactic anti-CMV drugs in patients with low CD4 counts is costly and is of questionable benefit in view of the side-effect profile of the drugs.

Management

Currently, licensed drugs used for the treatment of CMV include gancyclovir/valgancyclovir, cidofovir and foscarnet. Therapy for CMV retinitis includes an induction phase of gancyclovir 5 mg/kg BD followed by a maintenance phase of gancyclovir 5 mg/kg daily for 5 to 7 days per week. Alternative regimens include the use of intravenous foscarnet or cidofovir. The use of intraocular gancyclovir implants can be used to reduce the systemic side-effects of the drug, however systemic therapy is required to prevent damage to the contra-lateral eye.
The need for CMV maintenance therapy after completing 14 days of an induction phase in patients with CMV pneumonitis, colitis and hepatitis has not been established.

Herpes Simplex Virus

HSV-1 and HSV-2 are widely disseminated and can affect all populations.

Transmission

HSV-1 is transmitted primarily through contact with infected oral secretions; HSV-2 is acquired primarily through contact with infected genital secretions.

An HSV infected mother can transmit HSV to her infant, resulting in neonatal infection. Infection can occur by exposure to maternal genital fluids during labour and delivery, or by ascending infection. The risk for neonatal HSV infection is increased if there is genital shedding of HSV and if there is prolonged rupture of membranes. Risk is higher in an infant born to a woman who acquires HSV infection during pregnancy.[26]

In older children HSV transmission is through direct contact with infected oral secretions or lesions.

Clinical Manifestations

Neonatal HSV can present as a disseminated multiorgan disease, or can be localized disease involving the skin, eyes, and mouth. Infants with disseminated disease usually present at age 9 to 11 days. Vesicular rash occurs in approximately 80 percent of children with localized disease of the skin, eyes and mouth.[27] Infants with neonatal HSV infection are at risk for neurologic sequelae.

After the neonatal period, the most common presentation of HSV infection in children is orolabial disease characterized by a painful vesicular eruption with a few or many vesicles appearing on the lips, tongue, or buccal mucosa. Fever, irritability, and superficial painful ulcers are characteristic of primary HSV gingivostomatitis. The ulcers can interfere with feeding due to severe pain.

In HIV infected children, co infection with HSV can lead to extensive lesions, poor healing of ulcerative lesions, prolonged viral shedding, and dissemination. Sites of dissemination include the oesophagus, liver, lung, and CNS.

Diagnosis

Clinical diagnosis is based on the typical appearance of vesicles and ulcers. The virus can be isolated from the skin lesions by culture. Other detection methods include direct staining of infected cells for virus antigen, antibody detection, and identification of virus particles by electron microscopy. For children with suspected HSV encephalitis, detection of HSV DNA by PCR in the CSF is the diagnostic test of choice.

Treatment

Acyclovir is the drug of choice for treatment of local and disseminated HSV among infants and children. Neonatal HSV disease should be treated with high-dose IV acyclovir for 21 days. Orolabial lesions in HIV infected children can be treated with oral acyclovir for 7 to 14 days.

Most children can be treated on an outpatient basis. Repeated courses of treatment may be required. If there is super infection, use an appropriate antibiotic. It is important to be aware of the need for pain relief.

Admit the child if you suspect disseminated disease, or if the child is dehydrated. For inpatients, use of intravenous acyclovir is recommended.

Prevention

Preventing Exposure

Effective HAART regimens may decrease the shedding of virus in the maternal genital tract, thereby decreasing exposure. Use of acyclovir near term may also suppress shedding in late pregnancy. There are no proven ways to prevent exposure in children.[28] Primary prophylaxis against HSV disease is not recommended as the disease is easily treated.

Prevention of Recurrence

Because episodes of HSV disease can be treated successfully, chronic therapy with acyclovir is not required. However, children who have frequent or severe recurrences can be administered daily suppressive therapy with oral acyclovir. Effective HAART may decrease recurrences.[29]

Varicella-Zoster Virus

Epidemiology

Varicella-zoster virus belongs to the Herpes group of virus, and infections occur worldwide. Varicella causes greater morbidity and mortality in HIV-1 infected persons.[30]

Once established, VZV latency persists for life. Reactivation causes clinical zoster.

Transmission

VZV is transmitted mainly from skin lesions during illness but also can be transmitted through airborne spread. Varicella is highly contagious; clinical infection develops in about 80 percent of susceptible persons exposed in a household. Patients remain infectious until all vesicular lesions are crusted.

Mother-to-child transmission of VZV can occur, but is uncommon. If the varicella virus is transmitted to the fetus in late pregnancy, the newborn may develop acute neonatal varicella.

Zoster occurs only among persons previously infected with VZV.[30] HIV infected persons are at a much higher risk for zoster. Children who have lower CD4 counts during the primary varicella infection are more likely to develop zoster.[31] In addition, the lower the CD4 count, the more frequent the recurrences of zoster.

Clinical Manifestations

Varicella-zoster virus infection can cause primary infection (chickenpox) or reactivation of latent virus (shingles). The incubation period for varicella ranges from 10 to 21 days.

There is an initial period of fever and malaise, followed by an eruption of vesiculopapular lesions. The lesions are more numerous on the face and trunk than on the extremities, and are extremely itchy. Lesions evolve over 5 days through macular, papular, vesicular, pustular

and crust stages. Lesions in all stages of development are characteristic of varicella.

HIV infected children can have persistent chronic infection, with continued appearance of new VZV lesions for more than a month after primary or recurrent infection.

Complications of varicella include super infection of lesions with common organisms such as staphylococci or streptococci, pneumonia, and neurologic manifestations such as encephalitis and cerebellitis.[32]

The classical clinical presentation of zoster is a painful localized cutaneous vesicular eruption along one or more contiguous dermatomes. Lesions evolve over 1 to 2 days to form vesicles, pustules, and crusts. In HIV infected patients, zoster may be bullous, hemorrhagic, necrotic, and particularly painful.

Diagnosis

Varicella and zoster are diagnosed clinically by the typical appearance of generalized puritic vesicular rash of "chicken pox", and by the painful or puritic vesicular rash in a dermatomal pattern typical of zoster. In HIV infected children, where the rash may be atypical, skin biopsy may especially be useful.

Treatment

Acyclovir is the drug of choice for treating VZV infection in HIV infected children. For varicella, acyclovir should be initiated as soon as possible after initial lesions appear. New lesions can continue to appear for 72 hours after initiation of acyclovir and crusting of all lesions might take 5 to 7 days. IV acyclovir is recommended for treating primary varicella among HIV infected children with severe immunosuppression.

For the treatment of zoster, acyclovir must be given for 7 to 10 days. Longer duration of treatment may be required if the lesions are slow to resolve.

Initial IV administration should be considered for HIV infected children with severe immunosuppression. Pain control, in addition to antiviral therapy, is among primary clinical goals in HZ management.

Prevention

HIV infected children and adults who have no evidence of immunity to VZV should avoid exposure to persons with varicella or zoster.

Varicella vaccine is available for use mainly in the private sector in developing countries. Those who can afford the vaccine should be advised accordingly, i.e. in HIV infected children, if the age-specific CD4 is 15 to 24 percent, 2 doses of vaccine are given, starting at 12 months, and given at least 3 months apart.

For post-exposure prophylaxis against varicella, HIV infected children and adolescents who lack evidence of immunity to VZV should receive immunoglobulin as soon as possible and within 96 hours after close contact with a person with varicella or zoster.

Mycobacterial Infections

Nontuberculous Mycobacterium (NTM)

NTM or Mycobacterium other than Tuberculosis (MOTTS) refers to a group of mycobacterium (excluding *M. tuberculosis*) that causes disease particularly in severely immunocompromised patients.

The mycobacterium family of organisms has been divided into the following groups:

- ***Mycobacterium tuberculosis complex:***
  - Mycobacterium tuberculosis
  - Mycobacterium bovis (includes the vaccine strain Mycobacterium bovis BCG)
  - Mycobacterium africanum
- ***Nontuberculous Mycobacterium (NTM):***
  - Mycobacterium avium complex
  - Mycobacterium kansasii
  - Mycobacterium marinum
  - Mycobacterium ulcerans
  - Mycobacterium abscessus
  - Mycobacterium scrofulaceum

Mycobacterium Bovis BCG

Mycobacterium Bovis - Bacille Calmette-Guerin (BCG) is a live attenuated mycobacterium bovis vaccine strain. The original vaccine was developed by Pasteur in 1908 from a subculture of Mycobacterium Bovis, since then different strains of the vaccine have been developed, each with differing virulence and immunogenicity.

Over 100 million doses of BCG vaccine are given to infants annually worldwide (Fig. 2.13.2) predominately in areas with a high endemic tuberculosis burden. The BCG vaccine has been documented to protect against TB Meningitis and milliary TB in immune-competent young children; however the immunogenicity of the vaccine in immunocompromised children may be suboptimal and the vaccine does not protect against adult pulmonary tuberculosis. The rate of reported adverse events are extremely low in an immunocompetent population, with a 0.04 percent incidence of local reactions and 0.009 to 0.0002 percent incidence of disseminated disease. A retrospective audit of hospital records in a South African hospital over 2½ years identified 25 HIV infected or exposed infants with BCG disease, 32 percent had disseminated disease with a 100 percent mortality.[33] This high mortality rate has prompted the World Health Organization (WHO) to recommend that BCG be given to only HIV uninfected infants. However BCG is given at

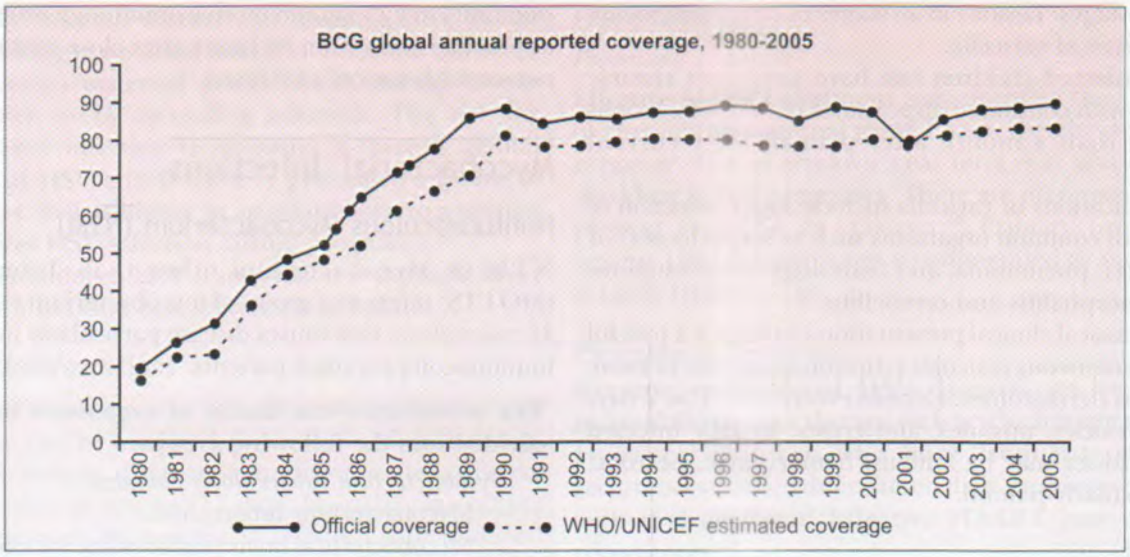


Fig. 2.13.2: Global BCG coverage





birth in most developing countries when the HIV status of the infant has not yet been confirmed making this recommendation difficult to implement in resource-limited settings.

Clinical Classifications

1. ***Talbot Classification***
   - ***Regional Disease:*** Persistent ulcer, abscess, fistula or lymph-adenopathy limited to inoculation site.
   - *Extra regional localized disease:* Infection at a single anatomical site, e.g. osteitis or cutaneous abscess outside the inoculation site.
   - ***Dissemination:*** All three of the following:
     - Isolation of BCG on culture and identification by biochemical methods
     - Dissemination: evidenced by either positive results of blood or bone marrow culture or evidence of infection at ≥2 anatomical sites beyond vaccination site
     - A systemic syndrome compatible with mycobacterial disease
   - ***Other BCG syndromes:*** Syndromes following vaccination in which bacteria are identified, e.g. Keloid formation/Uveitis (Probably immune-mediated)
2. ***Revised Pediatric Classification***[34]
   - ***Local BCG disease (Refer Figure along side):*** A local process at the site of vaccination. This includes any of the following:
   - BCG injection site abscess ^{3}10 mm × 10 mm
   - Severe BCG scar ulceration.
   - ***Regional disease:*** Involvement of any regional lymph nodes or other regional lesions beyond the vaccination site: Ipsilateral axillary, supraclavicular, cervical and upper arm glands. Lymph node

involvement includes enlargement, suppuration and fistula formation.

- ***Distant disease:*** Involvement of any site beyond a local or regional ipsilateral process. This includes any of the following: BCG confirmed from at least 1 distant site beyond the vaccination site, e.g. pulmonary secretions (gastric aspirates, tracheal aspirate), cerebrospinal fluid, urine, osteitis and distant skin lesion.
- ***Disseminated disease:*** BCG confirmed from >1 remote site beyond the vaccination site as above and/or from at least 1 bone marrow or blood culture.

BCG IRIS

Immune reconstitution inflammatory syndrome (BCG IRIS) is defined as BCG disease that presents in an HIV infected child within 3 months after the initiation of highly active antiretroviral treatment with/without immunological or viral proof of immune reconstitution. Identical criteria apply for localized, regional, distant and disseminated disease.

Dual disease: Dual disease with M. tuberculosis and *M. Bovis* BCG may occur especially in areas with high endemic TB burden.

Other BCG syndromes: Rare syndromes following vaccination in which bacteria are identified (e.g. keloid, formation and uveitis); these syndromes may have an immune basis.

Investigations

Kindly refer to Figure 2.13.3 for investigations of a patient with suspected BCG disease

Suspected BCG disease
All children <2 years with right-sided local or regional lesions that may indicate BCG disease.

In immunocompromised children, a high index of suspicion for primary distant or disseminated BCG disease should be maintained, even in the absence of local or regional BCG disease. Systemic symptoms may include fever of unknown origin.

↓

Suggested diagnostic work-up

A. All children
- Full history and clinical assessment, including detailed assessment and documentation of local and regional BCG lesions
- Fine needle aspirate for mycobacterial culture
- HIV testing

B. All HIV infected children or other suspected/proven immunodeficiency
- Chest radiography (antero-posterior and lateral)
- Minimum 2 gastric washings for mycobacterial culture
- Mycobacterial blood culture if febrile
- CD 4+ T lymphocyte count and viral load, if applicable and not done in prior 2 months
- Full blood and differential count
- Baseline liver function tests monitoring of toxicity
- Refer to infectious diseases service

C. Additional investigations for HIV-related and other immunodeficiencies with suspected distant or disseminate BCG disease
- As in A and B and
- Bone marrow aspirate/biopsy for mycobacterial culture
- Mycobacterial blood culture (even if afebrile)
- Abdominal ultrasound for intra-abdominal lymphadenopathy
- Radiography if osteitis is suspected
- Other systemic investigations as clinically indicated

BCG confirmation: *M. bovis* BCG confirmed by molecular[13] or culture and biochemical methods.[20]

Fig. 2.13.3: Investigations of a patient with suspected BCG disease[34]

Management[34]

HIV Uninfected Infants

Local or regional disease

Observe

- Consider therapeutic aspiration or excision biopsy especially if fluctuant node or abscess, persistent rapidly enlarging node or fistula formation or in the presence of a large injection site abscess.
- Report as vaccine-related adverse event to EPI.

Suspected or confirmed distant or disseminated disease

- *Treat medically:*
  - INH 15-20 mg/kg/day
  - Rifampicin 20 mg/kg/day
  - PZA 20-25 mg/kg/day (2 months or until TB excluded)
  - Ethambutol 20-25 mg/kg/day
  - Ofloxacin 15 mg/kg/day or ciprifloxacin 30 mg/kg/day
- Screen for immune function
- Monitor for drug toxicity
- Report as vaccine-related adverse event to EPI

HIV Infected or Immunocompromised Children

Local or regional disease:

- *Treat medically:*
  - INH 15-20 mg/kg/day
  - Rifampicin 20mg/kg/day
  - PZA 20-25 mg/kg/day (2 months or until TB excluded)
  - Ethambutol 20-25 mg/kg/day
  - Ofloxacin 15 mg/kg/day or ciprifloxacin 30 mg/kg/day
- Consider therapeutic aspiration if node fluctuant; 2 to 4 weekly follow-up: if no improvement or deterioration of adenitis consider excision biopsy.
- Monitor for drug toxicity
- Report as vaccine-related adverse event to EPI.

Suspected or confirmed distant or disseminated disease:

- Treat medically as above.
- Consider expedited HAART initiation
- Monitor for drug toxicity
- Report as vaccine-related adverse event to EPI

Regional BCG IRIS with no dissemination:

- Observe, regular follow-up for progression
- Report as vaccine-related adverse event to EPI

Mycobacterium Avium Complex

Microbiology

Mycobacterium Avium Complex (MAC) of organisms are ubiquitous environmental pathogens that can cause disease in susceptible individuals. The complex consists of at least 2 species, *M. Avium* and *M. Intracellulare* with M. Avium responsible for >95 percent of disseminated disease in patients with AIDS and M. Intracellulare causing predominately respiratory disease. Identification of MAC is based on physical and biochemical tests, while differentiation between the species requires specific DNA probes. MAC is a slow growing mycobacterium that requires 2 or more weeks to grow in culture. The mode of spread of MAC remains unclear, however colonization of the gastrointestinal and respiratory tract are the most likely sites of entry. After dissemination of the infection, MAC can be identified from blood, bone marrow, lymph nodes and liver and spleen. MAC has a wide geographic distribution and has been located in water, soil and in animals which act as environmental reservoirs of infection. Human to human spread of MAC has not been demonstrated.

Epidemiology

Despite the wide distribution of MAC in the environment, the rates of disseminated MAC in developing countries are reported far less than in North America and Europe. This apparent lower incidence may be in part due to the lack of diagnostic testing, particularly culture and genetic probe assays to detect MAC and the similar clinical presentation to *M. tuberculosis* infection. The higher incidence of *M.tuberculosis* and other virulent pathogens in developing countries may also result in a lower incidence of MAC infections. Disseminated MAC infection rarely occurs in patients with CD4 counts >100 cell/ml and typically occurs at a CD4 count of <50cells/ml. Other risk factors for MAC infection include high plasma HIV RNA levels (>100,000 copies/ml), previous OIs and previous colonization of the respiratory or gastro intestinal tract.[35]

Clinical Presentation

Patients with advanced HIV disease typically present with disseminated MAC infection. Initial symptoms are mild for several weeks with progressive fever, night sweats, weight loss or failure to maintain normal weight gain, fatigue, diarrhea and abdominal pain. On physical examination the signs are predominately localized to the abdomen, with hepatosplenomegaly, retroperitoneal or para-aortic lymphadenopathy forming a central abdominal mass and occasionally a doughy feeling abdomen.[36] Enlargement of the para-tracheal and peripheral lymph nodes have also been described. Associated laboratory abnormalities include anemia, leukopenia and thrombocytopenia.

Focal Lymphadenitis is more commonly associated with Immune Reconstitution Inflammatory Syndrome (IRIS). MAC IRIS usually presents within weeks to months of initiation of HAART with abdominal pain, fever and weight loss. MAC IRIS may be unmasking of an asymptomatic infection or worsening of symptoms of a previous MAC infection. A rising CD4 count and a falling HIV viral load differentiates MAC IRIS from ARV treatment failure with an opportunistic infection.

Laboratory Diagnosis

Diagnosis of MAC infection is made by the identification of MAC from normally sterile sites including blood culture, bone marrow, lymph node aspirate, stool and pulmonary secretions. MAC is an acid fast bacillus (AFB) and can be detected using the ZN Stain and Auramine stain. In areas with a high endemic incidence of tuberculosis, AFB positivity is treated as MTB without culture and sensitivity resulting in an under-detection of MAC infection. Isolation of MAC from culture of specimens from normally sterile sites confirms the diagnosis in the presence of compatible clinical signs and symptoms. Culture of MAC from blood culture, bone marrow and lymph node aspirates indicates disseminated disease. DNA probe assays can be used to both identify MAC and to identify the species.

MAC infection typically occurs in the clinical scenario of advanced HIV disease with severe immune-suppression (CD4 count <50 cells/μL).

Management

Drug management of disseminated MAC should include 2 or more active agents for duration of at least 18 months.

Recommended drugs include

Clarithromycin or Azithromycin (highly effective in decreasing the mycobacterial burden)

+

One of the following drugs:

Ethambutol

Rifabutin

Quinolone (moxifloxacin, ciprofloxacin or levofloxacin)

Injectable agents—amikacin or streptomycin.

In patients with advanced immunosuppression (CD4 cell count <50 cell/μL), high mycobacterial loads (>2 log^{10} colony forming units/ml) and not on HAART, a regimen consisting of 3 to 4 drugs is suggested. The initiation of HAART should be a priority for these patients; however, HAART should be delayed by up to 2 weeks after initiation of antimycobacterial treatment.

Parasitic Infections

Toxoplasma Gondii

Toxoplasma gondii is a parasitic protozoa, commonly found in cat feces, raw vegetables, and the soil.

Transmission

It is transmitted via raw or undercooked meat, particularly pork and lamb, and via cat feces. The major mode of transmission of *Toxoplasma gondii* infection among infants and young children is congenital.[37] Transmission is most likely to occur in infants of women who become infected during pregnancy.[38]

Clinical Manifestations

Most infants are asymptomatic at birth. Newborns may present with either generalized disease or predominantly neurologic disease. Infants infected in-utero are at high risk for toxoplasmosis encephalitis. Some infants may be born prematurely or are small for gestational age. Other signs and symptoms may include: fever, lymphadenopathy, jaundice, an unusually large or small head, skin rash, hepatosplenomegaly, etc. Neurological symptoms include seizures, hypotonia, hearing loss, retinitis, and mental retardation.

Diagnosis

Congenital toxoplasmosis can be diagnosed by EIA or an immunosorbent assay to detect Toxoplasma-specific IgM, IgA or IgE in neonatal serum within the first 6 months of life, or persistence of specific IgG antibody beyond 12 months of age.

With congenital toxoplasmosis, calcified lesions might be seen on skull X-ray, and a CT of the brain may show multiple, bilateral, ring-enhancing lesions.

Treatment of Disease

The preferred treatment for congenital toxoplasmosis is pyrimethamine combined with sulfadiazine, with supplementary folinic acid.

Preventing Exposure

All HIV infected children and their care givers should be counseled about sources of *T. gondii* infection. They should be advised not to eat raw or undercooked meat, and to avoid exposure to cats' feces. Washing of hands prior to eating and after playing with cats is mandatory.[25]

Prevention of Recurrence

Patients who have completed initial therapy for toxoplasmosis should be continued on therapy with lower doses of pyrimethamine and sulfadiazine. The WHO recommends that secondary prophylaxis may be stopped in children over 5 years of age if they have achieved a sustained increase in their CD4 counts with HAART.

Malaria

Few studies have examined the link between malaria and HIV in children (kindly refer to the chapter on HIV and Malaria coinfection in children for more details). It is thought that HIV infection increases rates of malaria fever and the severity of the disease. Malaria remains a burden in both Africa and India. Most infections are due to Falciparum or Vivax. A high index of suspicion is needed in areas where malaria is nonendemic and if there is a history of travel.

Considering that an estimated 1 billion people in South-East Asia are exposed to unstable malaria even small overlaps of malaria and HIV in these settings may have a large public health impact.

Transmission

Malaria is a disease caused by several species of Plasmodium, a parasite transmitted via mosquito bites. Pregnant women infected with both malaria and HIV are at higher risk of developing anemia, delivering a low birth weight infant, and delivering prematurely. Higher viral load increases the likelihood of maternal-to-child transmission (MTCT) of HIV. Malaria infection during pregnancy increases risks of MTCT in the intrauterine and intrapartum period as well as during the breastfeeding period.

Clinical Manifestations

Children under 2 years of age and those with lower CD4 counts are more likely to develop the severe form of disease and to have complications.

Early symptoms of malaria include irritability and drowsiness, followed by fever, rigors, and rapid breathing. Other symptoms of malaria include headache, nausea, and an enlarged spleen. Cerebral malaria may lead to convulsions and coma.

Diagnosis

Malaria is diagnosed by microscopic examination of a patient's blood. Blood smear examination remains the gold standard for laboratory confirmation of malaria. A Giemsa-stained thick blood smear is the most sensitive smear technique for detecting infection, while a thin blood smear is used for identifying the parasite.[39] A rapid malaria antigen-capture assay has been developed for use in children who are symptomatic. This test is of good

sensitivity and specificity for falciparum and ovale, but is not suitable for screening.

Treatment

Treatment of malaria is based on the severity of disease, patient's age at onset, parasite species, and known resistance patterns. HIV infection status does not affect choice of therapy.

Primary Prevention

Primary prevention remains cornerstone of control of infection. One of the most effective prevention strategies is the use of insecticide-treated nets over the bed, treatment of clothing, and the spraying of the insides of huts.[40] Cotrimoxazole provides a degree of protection against malaria. For persons traveling to endemic areas, prophylaxis is recommended, however, there is a potential for drug-drug interactions with HAART.

Cryptosporidium

Cryptosporidium is a protozoan parasite that causes persistent diarrhea and cholecystitis in immunocompromised patients. In humans, the main causes of disease are *C parvum and C hominis*. The organism is spread through the fecal-oral route, often through contaminated water. Cryptosporidium is spread by direct contact with infected adults, children in diapers, and infected animals. Food and water contaminated with feces can spread infection as well.

Clinical Manifestations

The disease can be asymptomatic or cause acute diarrhea or persistent diarrhea that can last for a few weeks. Symptoms include watery diarrhea (sometimes with mucus), abdominal pain and cramps, and a low grade fever. Patients with cryptosporidiosis may have frequent, watery, voluminous stools, sometimes lasting longer than 2 weeks.[40] In immunocompromised individuals, the symptoms are particularly severe. Many children will never completely eliminate cryptosporidium from their bodies.

Cryptosporidium can spread to the lungs, middle ear, pancreas, and stomach. The parasite can infect the biliary tract, causing cholecystitis and cholangitis.

Possible complications

- Cholangitis, cholecystitis
- Hepatitis
- Pancreatitis
- Severe malabsorption

Diagnosis

There are many diagnostic tests for cryptosporidium. They include microscopy, staining, and detection of antibodies. Microscopy can help identify oocysts in a fecal matter. Detecting antigens is another way of diagnosing infection, either with direct fluorescent antibody, or through indirect immunofluorescence assay. An ELISA test also detects antigens. Polymerase chain reaction (PCR) is another way to diagnose cryptosporidiosis. If the patient is thought to have biliary cryptosporidiosis then an ultrasound is recommended.

Treatment

Treatment is symptomatic, with fluid rehydration, electrolyte correction and management of any pain. In immunocompromised children, cryptosporidiosis resolves slowly and may cause progressively severe dehydration, electrolyte imbalances, malnutrition, wasting, and eventual death.

There is no reliable treatment for cryptosporidium enteritis.[41] Several drugs have been tried in the treatment, including paromomycin, atovaquone, nitazoxanide, and azithromycin are sometimes used. Nitazoxanide has been shown to shorten the duration of diarrhea, and can decrease the risk of mortality.[41] Metronidazole and azithromycin have been used to treat cryptosporidium with various degrees of success.[40] Effective HAART is the recommended treatment for cryptosporidium infections.[42]

Prevention

The best way to prevent cryptosporidiosis is to have good hygiene and sanitation. Prevention is through washing hands carefully after going to the bathroom or contacting stool, and before eating. Immunocompromised children must avoid contact with an animal feces and must avoid possibly contaminated food and water.

Case Studies

CASE 1

11/12 month female referred from peripheral hospital with the following problems:

- Multiple subcutaneous abscesses (Refer to the Figures on page 235)
- TB lymphadenitis, on TB Rx × 3 months
- BPN
- Marasmus (wt: 3 kg)
- RVD positive on ARVs × +/-6 months

Mother 20-year-old

- CD4 count – 503
- PMTCT – dual therapy (AZT/NVP) taken
- Mixed feeding – Exclusive Breastfeed for 2 days only





History

Date	Age	Diagnosis
Oct 08	1 month	BPN – Admitted to hospital
Jan 09	4 months	BPN – Admitted to hospital
Feb 09	5 months	BPN– Admitted to hospital, Auto-Immune Hemolytic Anemia (Coombs +ve) Transfused, polygam, prednisone, recurrent blood transfusions. PCR–done and referred for ARV work-up
March 09	6 months	Started on HAART – 3TC/d4T/LPV/r

Date	Age	Weight	Progress
June 09	8 months	3.55 kg	Left thigh abscess (treated with flucloxacillin)
July 09	9 months	3.75 kg	abscess right arm left thigh abscess still present but decreasing in size Started on Pulmonary TB treatment – Rif/INH/PZA
Aug 09	10 months	3.19 kg	BCG ulcer/ axillary abscess – ?TB Lymphadenitis- changed to 4 drug TB treatment - RIPE

Examination

General Exam: Ill looking, wasted
Multiple fluctuant abscesses:

Rt/Lt mandibular angles (1 cm)
Rt cervical region (3 cm)
Rt axilla, Rt elbow, Lt elbow (1 cm)
Lt and Rt inguinal region (2 cm)
Medial aspect of Lt Knee (0.5 cm)
Drained abscess on Lt upper thigh

Resp: RDS, Bilateral crepitations

CVS: Normal S1 S2 / no murmurs

Abdomen: Soft, Hepatomegaly 3 cm, soft, non tender. No splenomegaly/No other palpable masses

CNS: no meningism, increased tone globally, brisk reflexes

Blood results

FBC: Hb 7.9	WCC 17.3	Plts: 399
MCV 110	MCH 31	

U/E: 135/3.8/94/25/3.3/32

LFT: T Prot 60 alb 26 ALP 101 ALT 13
GGT 70

Pus swab TB Micro
- No AFB/Field + 11-20 pus cells

Fluid TB Microscopy auramine stain
- No AFB/Field + >20 pus cells

Gastric washing × 3
- Negative auramine

Aspirate AFB micro
- Ziehl-Neelsen positive
- Lt Cheek – AFB 3+ positive
- Rt Neck – AFB 2+ positive
- Rt Neck – AFB 2+ positive
- Rt Face – AFB 1+ positive

Haines Test (TB PCR) – Positive – Mycobacterium Bovis BCG

TB Culture – Negative

Assessment

- 11 months female
- RVD positive on ARVs × 6 months
  (clinical failure but immunological response)
- Disseminated BCGosis +/- Tuberculosis
- ? IRIS BCG/TB
- Marasmus

CASE 2

History

NS, 10 year-old female referred with problems of:

- HIV infection, WHO stage IV – on HAART (EFV, D4T, 3TC) since 02/12/2008.
- Presented with recurrence of abdominal pain and distension.
- Progressive loss of weight – over the last 4 months
- Past medical history:
  - Previous admission in February 2009 with persistent abdominal pain and distension – MOTT on stool culture – not speciated – Presumed to be Mycobacterium Avium Complex (MAC)
  - She had been commenced on anti- MAC treatment with clarithromycin, ethambutol, pyrazinamide in February 2009 (>1 year of treatment) + Bactrim and multivitamin
- Clinical response to treatment – weight increased and abdominal pain and distension improved.
- Despite this–poor immunological response–CD4 2.4 percent and a viral load <25 copies.

Baseline				
Date	6/10/2008	19/08/09	11/01/10	16/03/10
CD4 Count (abs)	5	23	53	17
CD4 %	0.34%	2.9%	2.62%	2%
Viral load	54000	<25	<25	<25

On Admission

On Examination

- emaciated, ill looking
- Anthropometry: Wasted and Stunted
  - *Wt:* 16 kg (49% of expected)
  - *Height:* 69 cm (86% of expected)
- pink, comfortable on room air
- well hydrated, unstable temperature
- papular urticaric rash with subcutaneous nodules

Systemic Exam

- ***Chest:*** no deformities or respiratory distress. Had normal breath sounds
- ***CVS:*** apex not displaced, normal heart sounds
- ***Abd:*** doughy abdomen with generalized abd tenderness. No guarding or rebound tenderness; 5 cm hepatomegaly – firm and nodular. No splenomegaly or ascites present.
- ***CNS:*** grossly intact

Assessment

- HIV infected child – on HAART with clinical and immunological failure despite virological suppression
- ***Recurrent Abdominal Symptoms:***
  - ? Recurrent intra-abdominal MAC
  - ? Intraabdominal TB (new or reactivation)
  - ? Malignancy - Lymphoma

Laboratory Investigations

- Stool AFB – AFB positive, Culture pending
- Parvo, EBV and CMV PCR negative
- CD4 count 2 percent absolute 17
- Viral load <25 copies
- ***Abdominal sonar:***
  - showed peripancreatic nodes
  - kidneys, spleen and pancreas normal
- ***CT scan abdomen:***
  - showed hepatosplenomegaly with extensive lymphadenopathy suggestive of TB or lymphoma.
- ***BMAT (Bone Marrow Aspiration Test)***
  - Megakaryocytes appear increased in number
  - Erythroid series was normoblastic
  - Myeloid series showed sequential maturation and hyperplasia
  - Iron stores increased to 4/6. No obvious infiltrates
  - ZN positive and PAS negative. Findings consistent with mycobacterium infection.
- ***Liver biopsy:*** showed granulomas with extensive AFB.
- ***Skin biopsy:*** features of active mycobacterium infection with numerous AFB. Auramine stain and 3 week culture negative.

Assessment

- Probable recurrence of Intra-abd MAC.
- Clinical/Immunological Failure with Virological suppression on HAART.

Key Messages

- Maintain a high index of suspicion
- Remember that children can get opportunistic infections even when the CD4 count is relatively normal
- A new opportunistic infection in a child on HAART is an indication of treatment failure
- Always consider carefully before starting a child on prolonged treatment, as with CMV infection.
- Review secondary prophylaxis, where applicable, in children on HAART who have good immunological responses
- Consider each child on an individual basis.

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2.14

HIV and Tuberculosis Co-infection in Children

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Tuberculosis (TB) represents a significant threat to child health, with children accounting for 15 percent of the global burden of TB. Human immunodeficiency virus (HIV) infection increases susceptibility to infection with *Mycobacterium tuberculosis*,the risk of progression from infection to TB disease as well as re-activation of latent TB. Increasing levels of co-infection with TB and HIV in children have been reported from countries with dual epidemics[1] with prevalence of HIV in TB infected children ranging from 10-60 percent.[2] Management of both infections poses a challenge to clinicians.

Epidemiology

Tuberculosis and HIV disease are leading causes of infectious disease associated mortality worldwide. Globally in 2007, there were an estimated 9.27 million incident and 13.7 million prevalent cases of TB with most of them in Asia (55%) and Africa (31%). The number of people living with HIV in 2007 included 30.8 million adults and 2 million children less than 15 years of age.[3] Approximately 14 percent of TB cases in 2007 were HIV positive; most of them living in Africa (79 percent) and South-East Asia (11%).[4] HIV infected individuals are estimated to be about 20 times more likely than HIV negative people to develop TB in endemic countries.[4] Studies have shown that young age and HIV infection are both risk factors for more severe, disseminated disease.[5] In high TB and HIV prevalent countries, new TB cases were highest among young adults—they are in close proximity with children, thus increasing their risk of exposure (Fig. 2.14.1).[4]

The lack of a gold standard for diagnosis is a major obstacle to accurately quantifying the true burden of childhood TB worldwide and the available estimates also do not reflect the diverse features of TB in children. Reported co-infection of HIV among children with TB in various Indian studies ranges from 2-68 percent but these estimates are likely to be biased because they are from tertiary enters.[6] Studies from sub-saharan Africa have shown co-infection rates of 11-64 percent in children—this is much higher compared to most Asian countries.[7] The mortality from AIDS (Acquired Immunodeficiency Syndrome) in children under 15 years of age was 270,000 in 2007.[3] TB was reported to be the third most common cause of death in HIV infected children with a clinical diagnosis of acute severe pneumonia.[8] Studies have also documented 6 times higher mortality in HIV infected children with TB compared to uninfected children.[9] TB often goes undetected during life as shown by the prevalence of TB in autopsy studies of HIV infected children which ranged from 1.3 to 18 percent.

Etiology

TB is a bacterial disease caused by organisms belonging to the *Mycobacterium tuberculosis* complex (tuberculosis, bovis, africanum and microti). These organisms are also

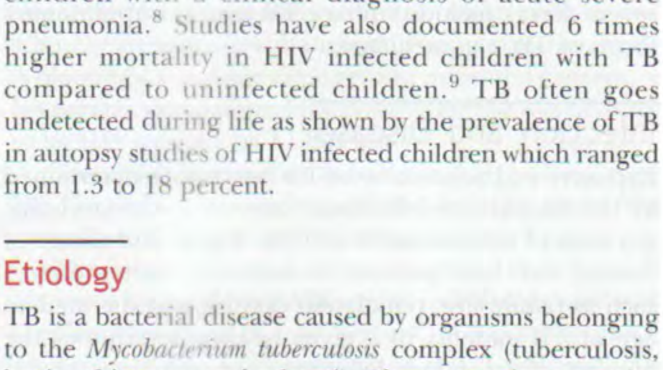


Fig. 2.14.1: New smear positive case notification rate by age, DOTS and Non DOTS, WHO 2007

Source: Global tuberculosis control–epidemiology, strategy, financing. WHO Report 2009. WHO/HTM/TB/2009.411.(http://www.who.int/tb/publications/global_report/2009/en/index.html)

known as tubercle bacilli (because they cause lesions called tubercles) or as acid-fast bacilli (AFB). Tuberculous infection occurs when a person harbours tubercle bacilli inside the body, but the bacteria are in small numbers and are dormant. These dormant bacteria are kept under control by the body's defences and do not cause disease. Many people have tuberculous infection and are well. Tuberculosis is a state in which one or more organs of the body become diseased as shown by clinical symptoms and signs. This is because the tubercle bacilli in the body have started to multiply and become numerous enough to overcome the body's defences.

Pathogenesis

TB disease in children is usually primary TB. The age when a child is infected determines the pattern of primary disease. Pulmonary disease in young children is closely linked to pathology of the mediastinal nodes. This is lymphobronchial TB, which results in a wide spectrum of segmental lesions. Young children (i.e. less than 5 years of age) are particularly susceptible to severe forms of disseminated disease following primary infection. These severe forms include miliary TB and extrapulmonary forms of TB, e.g. meningitis.

Infection and Disease

Exposure and acquisition of TB infection is determined by the number of infectious cases in the community, duration of infectiousness and the degree and nature of contact with such persons. In addition, various factors such as family size, population density, and the median age of TB patients in a given setting determines the number of secondary infections per infectious case.[12] Moreover the concentration of bacilli in the sputum of a TB case correlates well with the infectivity of the patient.[13] Infection in a child is indicative of recent transmission and is measured by conversion of the tuberculin skin test (TST).

The risk of developing disease once infected, is determined by various factors inclusive of age, nutritional and immune status of the child, genetic factors, virulence of the organism and size of infecting dose. Primary infection before 2 years of age progresses most frequently to serious disease within the first 12 months and the risk of disease progression decreases with advancing age (Fig. 2.14.2). Immunocompromised children experience a risk similar to that noted for very young children.[14] For infants the time span may be as short as 6 to 8 weeks.[15] The increased risk of TB among HIV positive children is partly attributable to immunosuppression as well as the fact that HIV infected children are more likely to be exposed to TB within their families. Even though

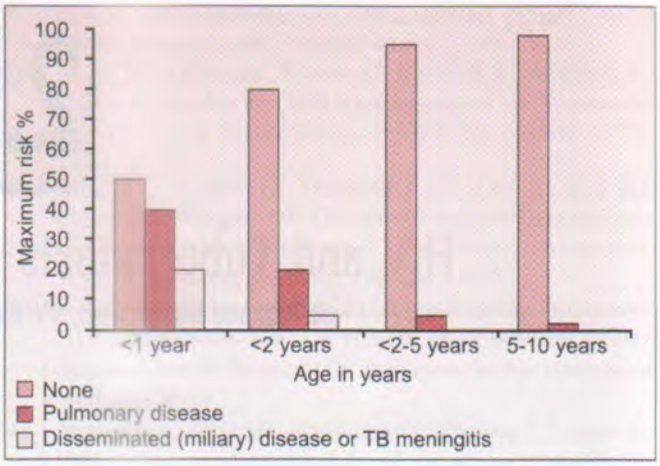


Fig. 2.14.2: Quantification of risk of progression from TB infection to disease based on the natural history of TB in children (Marais et al)

Source: Marais BJ, Gie RP, Schaaf HS, et al. The natural history of childhood intra-thoracic tuberculosis: A critical review of literature from the pre-chemotherapy era. Int J Tuberc Lung Dis 2004; 8(4):392-402.

HIV infected adults often have sputum smear negative TB, they still pose a considerable risk of transmission of TB infection of about 30-40 percent.[14] An equally important risk factor for childhood TB infection is poverty leading to under nutrition.[16] An important difference between adults and children is the timing of TB infection. In adults, latent TB infection (LTBI) is often acquired before HIV infection, and subsequent disease may represent a reactivation of a remote infection. On the contrary, most children are infected with HIV perinatally, and are only exposed and infected with TB at a later point in time. Young children with HIV are at high-risk of morbidity and mortality from other respiratory diseases (including PCP), and they may succumb to these infections before being infected with TB.[13]

As in adults, the natural history of TB in a child infected with HIV depends on the stage of HIV disease. Early in HIV infection, when immunity is good, the signs of TB are similar to those in a child without HIV infection. As HIV infection progresses and immunity declines, dissemination of TB becomes more common. Tuberculous meningitis, miliary TB, and widespread tuberculous lymphadenopathy occur.

Clinical Presentation

The most common clinical manifestations of pulmonary parenchymal disease and associated intrathoracic adeno pathy account for 60-80 percent of all cases.[17] The most common extrapulmonary manifestations are lymphaden-opathy (67%), followed by CNS involvement (13%) and

pleural (6%), miliary/disseminated (5%) and skeletal (4%) TB.[18] Though the clinical presentation of TB in HIV infected children is similar to that of uninfected, it is difficult to differentiate TB related symptoms from other HIV associated conditions.[19] Children with HIV often have other lung disease related to their HIV infection. Therefore, TB in an HIV infected child can be confused with lymphoid interstitial pneumonitis, bronchiectasis or any other lung infection. A recent autopsy study from Zambia found that the presence of multiple pathogens in a single child was common, and acute pyogenic pneumonia, *Pneumocystis carinii* pneumonia, tuberculosis and cytomegalovirus infection were the four most common findings overall.[20] Thus, there is a risk that TB could be over diagnosed in children (and they will be treated unnecessarily) and also that TB may be missed in an HIV infected child who improves with empiric antibiotics. Lymphoid interstitial pneumonitis (LIP) is the most difficult condition to distinguish from TB, due to radiographic similarities and clinical judgment is required to differentiate between the two (Table 2.14.1). Table 2.14.2 shows the differential diagnosis of respiratory illness while Table 2.14.3 shows the differential diagnosis of tuberculous meningitis in HIV infected children.

Malnutrition is a common condition in HIV infected children and is a major contributor to mortality in both HIV uninfected and HIV infected children. Malnutrition (both stunting and underweight) is highly prevalent among HIV infected children in India, at all ages and at all stages of HIV disease.[21] Conversely, HIV has been associated with nutritional disorders, and immune status and level of viral replication may be important in predicting growth outcomes.[22-24]

Growth (i.e. a composite of weight, length or height, and head circumference) is a sensitive indicator of optimal nutrition and of HIV disease progression. In HIV infected children, severe growth problems (i.e. growth failure and severe malnutrition not attributable to inadequate nutritional intake) may point to the need for ART to be initiated. Growth is also useful in the evaluation of the response to ART. Nutritional assessment, i.e. the systematic evaluation of current nutritional status, diet and nutrition-related symptoms, is critical in the early identification of malnutrition and poor growth as well as in the monitoring of HIV disease progression and treatment efficacy for children on ART. As for all infants, HIV infected infants should be measured monthly, ideally with the use of standardized growth curves. Thereafter, children should be weighed at each review and full nutritional assessments should be made every three months unless the child in question requires particular attention because of growth problems or special nutritional requirements.

Table 2.14.1: Clinical differentiation of miliary TB from LIP in children

	Miliary TB	*LIP*
Clinical Features		
Respiratory Symptoms	- / +	+ + +
Persistent Fever	+ +	+ +
Wasting	+ + +	- / +
Generalized Lymphadenopathy	- / +	+ + +
Parotid Enlargement	-	+ +
Clubbing	-	+
Hepatomegaly	+ +	+ +
CXR Features		
Diffuse Micronodular	+ +	+
Diffuse Reticular	-	+ +
Lymphadenopathy	- / +	+ +

Source: World Health Organization TB/HIV. A clinical manual. WHO/HTM/TB/2004.329 Geneva, Switzerland:WHO 2004

Case Report of LIP

A 3-year-old male child presented with recurrent respiratory infections and growth failure. On physical examination, the child was pale, had clubbing, weight 8.7 kg (Grade III malnutrition), bilateral cervical lymphadenopathy, crepitations over the right axillary and scapular areas on auscultation, and hepatosplenomegaly. A blood test was done after getting informed consent, as his parents were known HIV positive and he was detected to be HIV positive by ELISA test.

The child was classified as being in WHO clinical stage III. The child's chest radiograph showed right lower zone parenchymal lesions and Mantoux test was 0 mm.

The laboratory evaluations showed Hb 5.7gms/dl, Hepatitis B/C negative, WBC count 18,900 cells/mm^3 with a differential count of L 45 percent, M 9 percent, and G 46 percent. The CD4 percentage was 9 percent, CD4 count 765 cells/mm^3 and CD4/CD8 ratio 0.14. The child was started on antituberculous treatment (ATT) as there was no radiographic improvement after two weeks of antibiotics (Co-trimoxazole and Amoxicillin). In view of severe immunodeficiency (CD4 <15%) ART was initiated after the intensive phase of ATT had been completed.

After 3 months of ART (AZT+3TC+NVP) patient developed fever, severe cough and breathlessness and was admitted. Chest radiograph showed bilateral enlarged hilar nodes and diffuse nodular infiltrates and a diagnosis of LIP was made. He was treated with intravenous antibiotics and supportive care and improved. The initial diagnosis was probably LIP also and not TB.

Diagnosis of Tuberculosis in HIV+ Children

Establishment of an accurate diagnosis is a major challenge in childhood TB. The commonest type of TB in children is smear-negative PTB. This is because

Table 2.14.2: Differential diagnosis of respiratory illness in HIV infected children

Category of illness	*Causative agent(s)*	*Clinical features*	*Age ranges*	*Radiological features*	*Diagnostic technique*	*Treatment*[a]
TB	*M. tuberculosis*	Subacute onset,[b] persistent and unremitting cough, weight loss or failure to thrive, fever	All ages	Lymph node enlargement, infiltration, primary complex	Smear microscopy, gastric aspirate/ sputum culture, chest X-ray, tuberculin skin test, history of contact with source case, other tests where available	Anti-TB medications
Bacterial pneumonia	*Streptococcus pneumoniae, Hemophilus influenzae, Salmonella* spp. *Staphylococcus aureus, Klebsiella pneumoniae, Escherichia coli*	Rapid onset, high fever, elevated leukocyte count on full blood count	All ages	Bronchopneumonia	Sputum culture not useful in children; blood cultures	Broad-spectrum-antibiotics (including coverage of Gram negative organisms)
Viral pneumonia	Respiratory syncytial virus, adenovirus, influenza virus, cytomegalovirus, Epstein-Barr virus	Air trapping with wheezing	More common in infants than in older children	Diffuse interstitial infiltration, hyperinflation	Clinical	Supportive care
Lymphoid Interstitial pneumonitis	Immune response to Epstein-Barr virus	Slow onset, cough, mild hypoxia, associated generalized lymphadenopathy, parotid enlargement, clubbing	Older children	Diffuse reticulo-nodular pattern, lymph node enlargement	Clinical	Antiretroviral therapy, corticosteroids in some cases
Pneumocystis jirovecii pneumonia	Pneumocystis jirovecii	Abrupt, severe pneumonia, respiratory distress, severe hypoxia	Infants	Diffuse interstitial infiltration, hyperinflation	Clinical	Cotrimoxazole, corticosteroids for moderate to severe cases
Bronchiectasis	Recurrent respiratory infections (usually complication of lymphoid interstitial pneumonitis or TB)	Slow onset, cough productive of copious sputum (purulent, occasionally blood-stained), halitosis, finger clubbing	Older children	Honeycombing, usually of lower lobes	Chest X-ray	Physiotherapy, treatment of super infections, rarely lung resection (lobectomy)

[a] Note that in addition to the improvement of many of these conditions with the specific treatment indicated, their severity and frequency will often improve with antiretroviral therapy.

[b] Onset can occasionally be acute, especially in immunocompromised infants.

Source: World Health Organization (WHO). Guidance for National Tuberculosis Programmes on the management of Tuberculosis in Children (WHO/HTM/TB/2006.362) Geneva, Switzerland: WHO 2006

cavitating TB is infrequent and the majority of children with PTB are too young to provide a sputum specimen for smear microscopy. Therefore an alternative method of obtaining sputum, such as gastric aspiration, is required. If alternative diagnostic methods are not available or routinely practiced, the children are registered as having "smear-negative PTB", even though a smear has not been done. Smear-positive PTB is usually diagnosed in children older than 6 years. Figure 2.14.3 represents the diagnostic algorithm followed in RNTCP for the diagnosis of TB in children.[25] Studies have reported less than 10-15 percent of sputum smear positivity and 30-40 percent of culture positivity.[26, 27] Various specimen collection methods are shown in Table 2.14.4.[28]

The recommended approach to diagnose TB in children outlined by WHO includes careful history (including history of TB contact and symptoms consistent with TB), clinical examination (including growth assessment), tuberculin skin testing, bacteriological confirmation whenever possible, investigations relevant for suspected pulmonary TB (including chest X-Ray) and HIV testing (in high HIV prevalence areas).[29]

The next commonest type is extrapulmonary TB. Common forms of EPTB in children include: miliary TB and TB meningitis (usually in children less than 3 years

Table 2.14.3: Differential diagnosis of tuberculous meningitis

	CSF abnormalities			
Disease	*White Cells*	*Protein*	*Glucose*	*Microscopy*
Tuberculous meningitis	Elevated, L > PMN	Increased	Decreased	AFB (in some cases)
Cryptococcal meningitis	Elevated L > PMN	Increased	Decreased or normal	Positive India ink staining
Partially treated bacterial meningitis*	Elevated Variable ratio	Increased	Decreased	Bacteria on Gram stain (rarely)
Viral meningitis	Elevated L > PMN	Increased	Normal (low in mumps or H. simplex)	
Acute syphilis	Elevated L > PMN	Increased	Normal	
Late stage trypanosomiasis	Elevated L > PMN	Increased	Decreased	Motile trypanosomes
Tumour (carcinoma/ lymphoma)	Elevated L > PMN	Increased	Decreased	Leptospira
Amoebic meningitis	Elevated L > PMN	Increased	Decreased	Amoebae

PMN = polymorphonuclear leukocytes; L = lymphocytes

* Common differential diagnosis

Source: World Health Organization TB/HIV. A clinical manual. WHO/HTM/TB/2004.329 Geneva, Switzerland: WHO 2004

of age); TB lymphadenopathy (all ages); TB effusions (pleural, pericardial and peritoneal); and spinal TB (often school-aged children). The practical approach to diagnosis in extra-pulmonary TB is outlined in Table 2.14.5. The differential diagnosis of TB lymphadenopathy in HIV infection includes the following: persistent generalized lymphadenopathy (PGL), lymphoma, Kaposi sarcoma, carcinomatous metastases, sarcoid, and drug reactions (e.g. phenytoin). The diagnostic criteria for PGL

Table 2.14.5: Common forms of extrapulmonary TB in children

Site	*Practical approach to diagnosis*
Peripheral lymph nodes (especially cervical)	Lymph node biopsy or fine needle aspiration
Miliary TB (e.g. disseminated)	Chest X-ray and lumbar puncture (to test for meningitis)
TB meningitis	Lumbar puncture (and computerized tomography where available)
Pleural effusion (older children and adolescents)	Chest X-ray, pleural tap for biochemical analysis (protein and glucose concentrations), cell count and culture
Abdominal TB (e.g. peritoneal)	Abdominal ultrasound and ascitic tap
Osteoarticular	X-ray, joint tap or synovial biopsy
Pericardial TB	Ultrasound and pericardial tap

Source: World Health Organization (WHO). Guidance for National Tuberculosis Programmes on the management of Tuberculosis in Children (WHO/HTM/TB/2006.362) Geneva, Switzerland: WHO 2006

Table 2.14.4: Various specimen collection methods for TB diagnosis in children

Specimen collection method	*Problems/benefits*
Sputum	Not feasible in very young children; assistance and supervision may improve the quality of the specimen
Induced sputum	Increased yield compared with gastric aspirate, can be performed by trained nurses
Gastric aspirate	Difficult and invasive procedure; not easily performed on an outpatient basis; requires overnight fasting; sample collection advised on 3 consecutive days
Nasopharyngeal aspiration	Less invasive than gastric aspiration; no fasting required; comparable yield to gastric aspiration. To be considered in primary health-care clinics or on an outpatient basis
String test	Less invasive than gastric aspiration; tolerated well in children >4 years of age, bacteriological yield and feasibility require further investigation. Potential to become the routine sample collected in children who can swallow the capsule but can not produce a good-quality sputum specimen
Bronchoalveolar lavage (BAL)	Extremely invasive, only for use in patients who are intubated or who require diagnostic bronchoscopy
Urine/stool	Not invasive; excretion of Mycobacterium tuberculosis documented. To be considered with new sensitive bacteriological or antigen-based tests
Blood/bone marrow	Good sample sources, for diagnosis in the case of probable disseminated TB
Cerebrospinal fluid (CSF)	Fairly invasive; bacteriological yield low. To be considered if there are signs of tuberculous meningitis
Fine needle aspiration	Minimally invasive; excellent bacteriological yield, minimal side-effects. Procedure of choice in children with superficial lymphadenopathy

Source: Marais BJ and Pai M. New approaches and emerging technologies in the diagnosis of childhood tuberculosis. Ped Resp Rev 2007; 8: 124-133

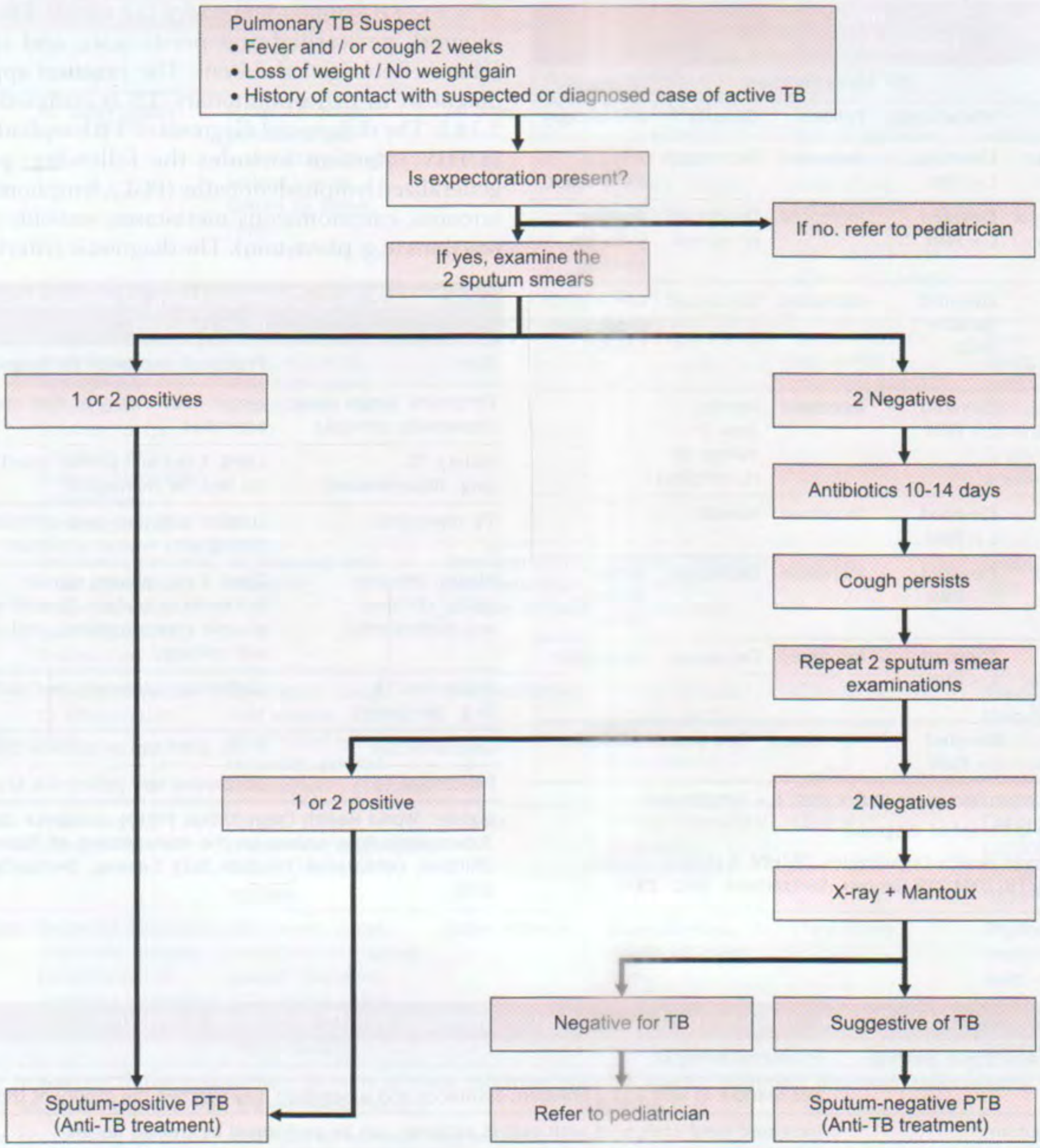


Fig. 2.14.3: Diagnosis of smear positive pulmonary TB. RNTCP New Guidelines, Effective from 1st April, 2009

are as follows: lymph nodes larger than 1 cm in diameter in 2 or more extra-inguinal sites for 3 or more months. The nodes are non-tender, symmetrical, and often involve the posterior cervical and epitrochlear nodes. The features of lymph nodes that indicate a need for further investigation, including biopsy, are: large (>4 cm diameter)[30] or rapidly growing lymph nodes, asymmetrical lymphadenopathy, tender/painful lymph nodes not associated with local infection, matted/fluctuant lymph nodes, obvious constitutional features (e.g. fever, night sweats, weight loss, hilar or mediastinal lymphadenopathy on CXR.

Treatment of Tuberculosis and Monitoring in HIV-TB Children

The treatment of TB includes a combination of the following anti-TB drugs namely: Isoniazid (I), Rifampicin

(R), Ethambutol (E) and Pyrazinamide (Z). Under the RNTCP, the regimen recommended for treating pediatric TB is the same as in adults ie $2EHRZ_3/4RH_3$. In early 2004, in consultation with Indian Academy of Pediatrics, the previous recommendations were revised whereby Ethambutol was included for treatment of pediatric cases even under 6 years of age, as a review found it to be quite safe.[31] The recommended dosages for the first line anti-TB drugs in children are shown in Table 2.14.6 and the RNTCP recommended regimens by category are shown in Table 2.14.7.[32]

Most current international guidelines recommend that TB in HIV infected children should be treated with a 6-month regimen as in HIV uninfected children. HIV infected children should be treated with rifampicin for the entire treatment duration. In RNTCP, all new TB cases known to be HIV positive are classified as seriously ill and treated with Category I regimen. Re-treatment cases are to be treated with Category II regimen and Category III should be avoided. Pediatric patient-wise boxes have been made available and children are treated by weight bands. Based on recent pharmacokinetic studies, the recommended dosage of rifampicin (RMP) is 10-15 mg/kg, isoniazid (INH) 10-20 mg/kg and ethambutol (EMB) 20 mg/kg.[33]

Table 2.14.6: Drugs used for the treatment of tuberculosis (from RNTCP guidelines for pediatric TB)

Drug	*Dosage*	*Adverse effects*	*Remarks*
INH	10-20 mg/kg /day PO OD	Hepatotoxicity, peripheral neuritis, mild CNS effects, Hypersensitivity reaction	Pyridoxine is recommended in HIV+ children
Rifampicin	10-15 mg/kg/ day PO OD	Stains urine, tears, sweat, contact lenses and other body fluids orange. GI upset, skin rash, hepatitis, thrombocytopenia, cholestatic jaundice	Rifampicin accelerates clearance of PIs and NNRTIs resulting in sub therapeutic levels
Pyrazinamide	30-35 mg/ kg/day PO OD	Hepatotoxicity, hyperuricemia, arthralgia, skin rash, GI intolerance	
Ethambutol	20-30 mg/kg/ day PO OD	Optic neuritis, color blindness, headache, nausea, peripheral neuropathy, rash, hyperuricemia	Monthly evaluation of vision is recommended
Streptomycin	15 mg/kg /day IM	Ototoxicity and nephrotoxicity	

Source: Guidelines for HIV care and treatment in infants and children. NACO and IAP. November 2006

Table 2.14.7: RNTCP recommended treatment regimen according to category

Category of treatment	*Type of patients*	*Intensive phase*	*Continuation phase*
Category I	New sputum smear-positive PTB* New sputum smear-negative PTB and extrapulmonary TB, Seriously ill*	$2\ H_3R_3Z_3E_3$***	$4\ H_3R_3$
Category II	Sputum smear-positive or negative relapse, treatment failure and treatment after default	$2\ S_3H_3R_3Z_3E_3 + 1\ H_3R_3Z_3E_3$	$5\ H_3R_3E_3$
Category III	New sputum smear-negative and extrapulmonary TB, not seriously ill**	$2H_3R_3Z_3$	$4\ H_3R_3$

* In seriously ill children, sputum smear negative PTB includes all forms of sputum smear-negative PTB other than primary complex. Seriously ill EPTB includes TB meningitis (TBM), disseminated TB, TB pericarditis, TB peritonitis and intestinal TB, bilateral extensive pleurisy, spinal TB with or without neurological complications, genitorurinary TB, and bone and joint TB.

** Not seriously ill sputum smear-negative PTB includes primary complex. Not seriously ill EPTB includes lymph node TB and unilateral pleural effusion.

*** The number before the letters refers to the number of months of treatment (prefix). The subscript after the letters refers to the number of doses per week.In patients with TBM on category treatment, 4 drugs used during the intensive phase should be HRZS (instead of HRZE). Continuation phase of treatment in TBM and spinal TB with neurological complications should be given for 6-7 months, thus extending the total duration to 8-9 months. Steroids should be used initially in hospitalized cases of TBM and TB pericarditis and reduced gradually over 6-8 weeks.

Source: Guidelines for HIV care and treatment in infants and children. NACO and IAP. November 2006

Since isolation of M.TB either by smear or culture is rare, treatment response is often judged on clinical criteria such as symptom amelioration, weight gain or regression of radiographic findings which however changes slowly.[34] Wherever possible, follow-up sputum examinations should be performed at the same frequency as in adults.

Considerations for the Timing of ART Initiation Following the Initiation of Rifampicin-Containing TB Treatment

The co-management of TB and HIV is complicated by drug interactions, particularly rifampicin with the Non Nucleoside Reverse Transcriptase Inhibitor (NNRTI) and Protease Inhibitor (PI) classes. Because rifampicin is an inducer of the cytochrome p450 enzyme system, co-administration results in sub-therapeutic antiretroviral drug levels. Further, overlapping toxicity profiles may result in an increased risk of cutaneous or hepatic toxicity. The choice of ART regimen in TB/HIV co-infected children is also complicated by the limited options for pediatric drug formulations and/or dosing information (particularly for children under 3 years of age) for antiretroviral drugs. Among children with co-infection, initiation of anti-TB treatment is a priority, as pulmonary TB is a WHO stage III disease while extrapulmonary TB is stage IV. The decision to initiate ART should take into consideration the degree of immune suppression and the child's progress during anti-TB treatment.[35]

Table 2.14.8 shows the recommendations for the timing of ART following the initiation of anti-TB treatment in children who are coinfected with HIV.[32] Where possible, the initiation of ART should be deferred

Table 2.14.8: Recommendations for the timing of ART following the initiation of TB treatment with a rifampicin-containing regimen in HIV infected infants and children

Clinical Stage of child with TB (as an event indicating need for ART)	*Timing of ART following initiation of TB treatment (rifampicin-containing regimen)[a]*	*Recommended ARV regimen[c]*
WHO pediatric clinical stage 4[b]	Start ART soon after initiating TB treatment (between 2 and 8 weeks)	**In children <3 years:** Standard first-line regimen of 2 NRTIs + NVP[d]
	With clinical management alone:	**In children >3 years:**
	Start ART soon after initiating TB treatment (between 2 and 8 weeks)	Standard first-line regimen of 2 NRTIs + EFV[e]
	If excellent clinical response to TB treatment in first 2 to 8 weeks of TB therapy, and child is stable and on co-trimoxazole preventive therapy (CPT),[a] it may be reasonable to delay initiation of ART	
WHO pediatric clinical stage 3[c]	**Where CD4 is available:**	Following completion of TB treatment,
	Evaluate possibility to delay initiation of ART depending on assessment of clinical status and CD4 cells, and clinical and immunological response to TB therapy:	it is recommended to change from EFV to NVP after 2 weeks of completion of ATT unless other contraindications.
	Severe and advanced immunodeficiency:[f] Initiate ART soon after initiating TB treatment (between 2 and 8 weeks)	Regimens as recommended above
	Mild or no immunodeficiency:[g] Initiation of ART may be delayed until after the completion of TB therapy; closely monitor response to TB therapy and reassess need for ART after TB therapy; if no improvement, consider starting ART	Where ART can be delayed until after completion of TB treatment, initiation with a standard two NRTIs + NNRTI first-line regimen is recommended

Notes:

a Administration of CPT is important in children with TB/HIV coinfection.

b All children with pediatric clinical stage 4 should be initiated on ART regardless of CD4 cell count/% criteria.

c Except for lymph node TB

d Careful clinical monitoring with laboratory support, if available, is recommended where NVP is administered concurrently with rifampicin.

e EFV is not currently recommended for children <3 years of age or < 10 kg and should not be given to postpubertal adolescent girls who are either in the first trimester of pregnancy or are sexually active and not using adequate contraception.

f Severe immunodeficiency; advanced immunodeficiency is assumed to be up to 5% above the age-specific CD4 threshold for severe immunodeficiency or CD4 200-349 cells/mm^3 for children ≥ 5 years of age.

g Mild or nonsignificant immunodeficiency is assumed at age specific CD4 levels above those defining advanced immunodeficiency.

Source: Guidelines for HIV care and treatment in infants and children. NACO and IAP. November 2006

for at least 2 to 8 weeks in children starting anti-TB treatment. A careful review of any possible drug interactions between ART and anti-TB medications should be carried out.

Considerations for the Choice of First-line ARV Regimens in Children Receiving Rifampicin-containing TB Treatment

In children over 3 years of age a standard first-line regimen of two NRTIs [Zidovudine (AZT) or Stavudine (d4T) with Lamivudine (3TC)] + Efavirenz (EFV) [the NNRTI component] is suggested. In children under 3 years of age, Nevirapine should be used as Efavirenz is contra-indicated – dosing should be on the higher side (of the range of 150-200mg/kg/dose) and close monitoring should be performed for hepatic toxicity. An alternative is the triple NRTI regimen (i.e. d4T or AZT+3TC+ ABC). Though this combination had lower virological potency than an EFV-based regimen in adults, because of concern about the potential for sub-therapeutic dosing of NNRTIs with concomitant rifampicin, a triple NRTI regimen could be a good choice in this situation. Because of concerns related to teratogenicity, EFV should also be avoided in adolescent girls of childbearing potential (without adequate contraception) or who are in the first trimester of pregnancy.

Considerations for Children on First-line ARV Regimens Diagnosed with TB

ART should continue in children already on a first-line regimen who are subsequently diagnosed with TB. However, the ARV regimen should be reviewed and may need adjustment in order to ensure optimal treatment of both TB and HIV and to decrease the potential for toxicities and drug-drug interactions. In children receiving a standard first-line regimen of two NRTIs + Efavirenz and where TB has occurred, the same regimen can be continued. Recent data suggests that among children on NVP-based regimens, the response to treatment is similar to patients not taking rifampicin. Because of overlapping toxicities and drug-drug interactions, children who are given rifampicin and NVP concomitantly should be followed up more frequently and laboratory parameters, if available, should be checked.

Considerations for Children on Second-line ARV Regimens Diagnosed with TB

For children who are receiving a second-line regimen with RTV (ritonavir)-boosted PIs and are diagnosed with TB, the choice of ARV regimens is more difficult because of likely resistance to first-line NRTI drugs and varying interactions between rifampicin and the PIs. Single PIs, and PIs given with low dose RTV(r) boosting, are not recommended to be administered with rifampicin because of the substantial (>70%) decrease in PI drug levels. The use of SQV (Saquanavir) with higher-dose (i.e. full-dose) RTV boosting has been suggested, but, because of significant hepatocellular toxicity observed in adults receiving this combination with rifampicin, it is not recommended. Although there are no efficacy data, LPV (Lopinavir)/r could be administered with additional RTV dosing to provide standard therapeutic doses of RTV; a dose increase to the same level as the LPV dose in mg may be considered (i.e. LPV200/RTV200). The use of other boosted PI combinations is discouraged until further data become available. NFV (Nelfinavir) should not be administered with rifampicin.[36]

Studies have documented poorer treatment outcomes and higher mortality among HIV infected children with TB. The possible reasons include higher incidence of co-infections with other pathogens, malabsorption and lower levels of anti-TB drugs, misdiagnosis of TB in children due to HIV related lung diseases, presence of underlying chronic lung disease, poor adherence to treatment due to associated illness or death of parents, advanced immunosuppression and severe malnutrition.[37] A prospective cohort of children with TB found that HIV positive children were younger, more underweight and had a 6-fold higher mortality as well as a decreased cure rate compared to HIV negative children.[38] Experience from the Tuberculosis Research Center in Chennai, India also suggests that TB manifestations were more severe in HIV positive children with lower cure rates and higher mortality.[39]

HAART has benefits not only in reducing TB morbidity and mortality but in reducing future incidence of TB. The number of TB cases per 100 patient years was 53.3 during the 9 months prior to HAART initiation, and 6.4 during post HAART follow-up.[40] Among children initiated on HAART, the 6-month probability of survival was 0.86 in the active TB group, 0.94 in the past history of TB group and 0.89 in the non-TB group. Thus, HIV infected children with active and previous TB who are started on ART have good outcomes that are similar to those of children started on ART due to a non-TB diagnosis.[41]

The Role of Adjuvant Steroid Treatment

Adjuvant steroid treatment is steroid treatment given in addition to anti-TB drug treatment.

Indications for treatment with steroids:

- TB meningitis (decreased consciousness, neurological defects, or spinal block)
- TB pericarditis (with effusion or constriction)
- TB pleural effusion (when large with severe symptoms)
- Hypoadrenalism (TB of adrenal glands)

- TB laryngitis (with life-threatening airway obstruction)
- Severe hypersensitivity reactions to anti-TB drugs
- Renal tract TB (to prevent ureteric scarring)
- Massive lymph node enlargement with pressure effects on airway.

Steroids are immunosuppressant and may further depress immunity and increase risk of opportunistic infections in HIV positive patients. However, on balance, TB/HIV patients are still likely to benefit from the use of steroids for the above indications.

Immune Reconstitution Inflammatory Syndrome (IRIS)

Immune reconstitution inflammatory syndrome, characterized by clinical deterioration after initial improvement, is frequently observed in patients on anti-TB treatment who initiate ART. The reaction occurs during the first 3-6 months of ART, presents with paradoxical deterioration of symptoms and signs, is generally self-limiting and can be managed with anti-inflammatory agents. Sometimes a child on ART may develop *TB de novo* and this requires ATT. [35]

Immunoprophylaxis with BCG Vaccination

BCG (Bacille Calmette Guerin) is a live attenuated vaccine derived from *Mycobacterium bovis* and has been given to children since the 1920s. It is included in the immunization programme of most TB endemic countries and is administered to children at birth. A meta-analyses indicated a consistent BCG induced protective efficacy in young non-HIV infected children against disseminated forms of TB with a summary estimate protective effect of 73 percent (67-79%) against TB meningitis and 77 percent (58-87%) against miliary disease.[42] There is no evidence of any BCG-induced protective effect in HIV infected children. On the contrary, studies have documented BCG induced disease and adverse reactions. A retrospective, hospital-based study from South Africa identified BCG induced disease in 25 children between 2002-05 among whom 17 were HIV infected with disseminated disease in 6 children with high mortality. The study concluded that BCG vaccination poses a risk to infants perinatally infected with HIV and to other primary immunodeficient children. Following a review of relevant data emerging over the last years, the Global Advisory Committee on Vaccine Safety (GACVS) and the Strategic Advisory Group of Experts (SAGE) therefore recommended revising previous WHO recommendations, making known HIV infection in infants a full contraindication for BCG vaccination, even in settings highly endemic for TB.[43]

Chemoprophylaxis

Preventive therapy (chemoprophylaxis) is given to prevent progression of latent infection to TB disease. Current WHO guidelines advise that all children <5 years of age who are in close contact with a sputum smear positive index case should be actively traced, screened for TB, and provided preventive chemotherapy once active TB has been excluded.[44] The fact that the majority of transmission in children <3 years of age occurs in the household, while they are also the group at highest risk of progressing to disease following primary infection with M.TB, emphasizes the particular importance of active contact tracing and the provision of preventive chemotherapy in high-risk children.[45] The most widely used drug for preventive therapy is INH. This is based on trials that have established the efficacy of INH in preventing TB in adult patients with latent infection.[46,47] INH preventive therapy is recommended for HIV infected children if living in high TB prevalence areas or who are household contacts of TB patients.[48] INH preventive therapy has shown early and significant survival benefits and reduction in TB incidence in HIV infected children.[49] The current recommendations from RNTCP and IAP are 6 months of INH based on studies from developed countries. There is no data on the optimal duration of INH preventive therapy for children in a developing TB endemic country. INH prophylaxis in HIV infected children has the potential to play a major public health role by reducing TB incidence and death. A recent Cochrane review identified one randomized clinical trial in which 263 HIV infected children were randomized to INH and cotrimoxazole or placebo and cotrimoxazole, given daily or three times a week. The trial showed a marked reduction in TB incidence (3.8% vs 9.9%) and death (8% vs 16%) in the INH group.[50]

Drug Resistant TB in Children

There were an estimated 0.5 million cases of multidrug-resistant TB (MDR-TB) in 2007. By the end of 2008, 55 countries and territories had reported at least one case of extensively drug-resistant TB (XDR-TB).[51] Comprehensive studies on resistance to anti-TB drugs in children are limited. Surveillance of Antituberculosis Drug Resistance from 2005-07 among children from South Africa showed a significant rise from previous surveys-resistance to isoniazid or rifampin increased from 6.9 percent to 12.9 percent to 15.1 percent and multidrug resistance from 2.3 percent to 5.6 percent to 6.7 percent.[52] Drug resistance among children has been documented in both pulmonary and extrapulmonary clinical trials.[53] MDR-TB requires prolonged treatment duration of

24 months with 2nd line drugs which are more toxic. According to the 2006 WHO guidelines for programmatic management of drug resistant TB, the treatment of MDR-TB treatment includes a fluoro quinolone, an injectable (capreomycin, kanamycin or amikacin), at least 2 drugs of the following; cycloserine, thiomides and para-amino salicylic acid and first line agents other than INH and RIF to which the patient isolate is susceptible. [54] The mode of action and side effects of second line antituberculosis drugs are given in Table 2.14.9 [44] and their dosage in children is shown in Table 2.14.10.[54] The diagnosis of pediatric MDR-TB is often extremely delayed due to reliance on the adult case definition; a high index of suspicion should facilitate earlier diagnosis and treatment of pediatric MDR-TB.[55] Thirty eight children in Peru were treated with supervised, individualized regimens consisting of 5 or more drugs, within the national program. Despite half of them being anemic and malnourished, treatment was well tolerated and resulted in a 95 percent cure rate.[56]

Case Studies

CASE 1

A 12-year-old boy with a history of HIV infection presents to the emergency department with progressive shortness of breath and dyspnea on exertion for the past month. He also complains of productive cough with white sputum and fever. The patient reports no chest pain, hemoptysis, orthopnea, paroxysmal nocturnal dyspnea, palpitations, or lower-extremity swelling. He does not report any recent travel or sick contacts. He has taken no medications recently.

On physical examination, the patient's temperature is 101.0°F (38.3°C). His pulse rate is 136 beats/min, with a regular rhythm. His blood pressure is 100/70 mm Hg. The patient's respiratory rate is 30 breaths/min, with an oxygen saturation of 76 percent while breathing room air. In general, the patient is cachectic and dyspneic. He has dry mucous membranes, with removable white plaques throughout the oropharynx. The remaining head and neck examination is normal. Coarse bibasilar crackles are present on auscultation. His chest is nontender on palpation, is resonant to percussion, and expands symmetrically. Except for tachycardia, the cardiac examination is normal. The abdominal and neurologic examinations are normal. The patient has no cyanosis, clubbing, or edema of the extremities. There was insignificant palpable lymphadenopathy.

The electrocardiogram shows sinus tachycardia. The chest X-ray shows diffuse, bilateral increased interstitial markings. The white blood cell count is $3.6 \times 10^3/\mu L$. The CD4 lymphocyte count is 54 cells/μL. An induced sputum specimen is sent for analysis.

Table 2.14.9: Second-line anti-TB drugs for treatment of MDR-TB in children

Drug	*Mode of action*	*Common side effects*
Ethionamide or prothionamide	Bactericidal	Vomiting, gastrointestinal upset[a]
Fluoroquinolones[b]		Arthropathy, arthritis
Ofloxacin	Bactericidal	
Levofloxacin	Bactericidal	
Moxifloxacin	Bactericidal	
Gatifloxacin	Bactericidal	
Aminoglycosides		Ototoxicity, hepatotoxicity
Kanamycin	Bactericidal	
Amikacin	Bactericidal	
Capreomycin	Bactericidal	
Cycloserine or teridazone	Bacteriostatic	Psychiatric, neurological

MDR, multidrug-resistant.

a This can be overcome by initially dividing the daily dose and starting with a lower dose for the first week or two.

b Although fluoroquinolones are not approved for use in children in most countries, the benefit of treating children with MDR-TB with a fluoroquinolone may outweigh the risk in many instances.

Source: World Health Organization. Guidance for National tuberculosis programs on the management of tuberculosis in children.(WHO/HTM/TB/2006.362) Geneva, Switzerland: WHO 2006

Table 2.14.10: Pediatric dosing of second-line antituberculosis drugs

Drug	*Daily dose (mg/kg)*	*Frequency*	*Maximum daily dose*
Streptomycin	20-40	Once daily	1 g
Kanamycin	15-30	Once daily	1 g
Amikacin	15-22.5	Once daily	1 g
Capreomycin	15-30	Once daily	1 g
Ofloxacin	15-20	Twice daily	800 mg
Levofloxacin	7.5-10	Once daily	750 mg
Moxifloxacin	7.5-10	Once daily	400 mg
Ethionamide	15-20	Twice daily	1 g
Prothionamide	15-20	Twice daily	1 g
Cycloserine	10-20	Once or Twice daily	1 g
P-aminosalicylic acid	150	Twice or thrice daily	12 g

Source: World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. (WHO/HTM/TB/2008.402) Geneva, Switzerland: WHO 2008

What is the likely diagnosis?

1. Pulmonary tuberculosis
2. Kaposi's sarcoma
3. Lymphoma

4. *Pneumocystis jirovecii* pneumonia
5. *Cryptococcus neoformans* pneumonia

Answer is 4

The diagnosis of *Pneumocystis jirovecii* pneumonia (PCP) was based on the patient's history, physical examination, chest X-ray, and sputum microscopic examination.

The induced sputum sample was negative for AFB as well as for Pneumocystis.

The patient received trimethoprim-sulfamethoxazole therapy for 21 days.

Which of the following statements concerning prophylactic therapy for *Pneumocystis jiroveci* is true?

1. Prophylaxis should be started and continued for the lifetime of the patient.
2. Prophylaxis should be started and discontinued once the patient's CD4 count is above 100 cells/μL.
3. Prophylaxis with trimethoprim-sulfamethoxazole should be avoided in patients using methotrexate because of the risk for severe myelosuppression.
4. Prophylaxis should be started and discontinued in accordance with age specific CD4 cut offs.

Answer is 4

For infants and children one through four years of age, initiation of co-trimoxazole prophylaxis is recommended if the child has WHO clinical stages 2, 3 or 4, regardless of CD4 percentage, or if the child has a CD4 percentage <25 at any WHO stage. For children 5 years of age or older, WHO adult guidelines should be followed. (Any WHO clinical stage and CD4< 350 cells per mm^3 or WHO clinical stage 3 or 4 irrespective of CD4).

Case 2

A 2-year-old boy with a history of HIV infection presents to the pediatric department with cough, rise of temperature and loss of appetite for the past 2 weeks. He has a productive cough with white sputum. The patient also reports of dyspnea but no palpitations, or lower-extremity swelling. He was not on any medications. The patient had no known drug allergies.

On physical examination, the patient's temperature is 38.1°C. His pulse rate is 110 beats/min, with a regular rhythm. His blood pressure is 100/70 mm Hg. The patient's respiratory rate is 29 breaths/min. The patient has no cyanosis, clubbing, or edema of the extremities. His chest is nontender on palpation, is resonant to percussion, and expands symmetrically. Coarse crackles are present on auscultation. The cardiac examination and abdominal examination is normal. There is no focal neurological deficit.

The white blood cell count is 11.2 × 10^3/µL. The CD4 lymphocyte count is 54 cells/µL. A chest X-ray shows left lower lobe consolidation. CT Thorax shows left lower consolidation with minimal pleural effusion. His gastric lavage smear was positive on AFB examination. The patient needs to be started both on ATT and ART.

What is the Line of Management?

1. Consider delaying start of ART until anti-TB treatment is completed.
2. Start ART between 2 and 8 weeks following start of anti-TB treatment.
3. Start ATT and ART together.

Answer is 2

According to WHO guidelines 2010, all HIV infected patients with TB should be started on ART as soon as possible. Where possible, the initiation of ART should be deferred for at least 2–8 weeks in children starting anti-TB treatment who have not yet started ART (e.g. antiretroviral "naive" patients). A careful review of any possible drug interactions between ART and anti-TB medications should be carried out.

What is the preferred ART regimen?

1. AZT + 3TC + ABC
2. Two NRTIs + EFV
3. Two NRTIs + NVP

Answer is 1

(If ABC is not available, 2 NRTIs with NVP may be used but NVP should be dosed at the upper end of its dosing range).

Rifampicin stimulates the activity of the cytochrome P450 liver enzyme system, which metabolizes PIs and NNRTIs. This can lead to decreased blood levels of PIs and NNRTIs especially Nevirapine. The potential drug interactions may result in ineffectiveness of ARV drugs or an increased risk of drug toxicity. EFV is not currently recommended for children <3 years of age.

Key Messages

- HIV infection increases susceptibility to infection with *Mycobacterium tuberculosis*, the risk of progression from infection to TB disease as well as re-activation of latent TB
- The lack of a gold standard for diagnosis is a major obstacle to accurately quantifying the true burden of childhood TB worldwide
- Differential diagnosis of TB includes *Pneumocystis jiroveccii* pneumonia, bacterial pneumonia and lymphocytic interstitial pneumonitis
- The co-management of TB and HIV is complicated by drug interactions, particularly rifampicin with the NNRTI and PI classes

- The decision to initiate ART should take into consideration the degree of immune suppression and the child's progress during anti-TB treatment.

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2.15

Hepatitis B Co-infection in HIV Infected Individuals with Special Reference to Children

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Introduction

Hepatitis B is caused by the hepatitis B virus (HBV), consisting of a small, circular, partially double-stranded DNA molecule within the *Hepadnaviridae* family. The global singular epidemics of HIV and HBV have resulted in valuable data that has adumbrated dynamics of interaction between these two disease entities.

The dreadful consequences of co-infection are variegated and include increased hepatic morbidity and mortality, as well as increased HBV viral replication, and hepatotoxic side effects of antiretroviral drugs. There are other relevant phenomena, such as the risk of immune reconstitution-related exacerbation of HBV secondary to highly active antiretroviral therapy (HAART). This is especially important in regions with high rates of simultaneous infections.

Epidemiology

HBV is a highly contagious DNA virus with a 3 percent overall risk of infection and is tenfold more infectious than HCV (0.3% risk) and about 100 times more infectious than HIV (0.03% risk). It is estimated that more than 2 billion people are currently infected with HBV worldwide and of these, approximately 350 million have manifestations of chronic infection and risk of serious illness.[1-3] The risk of progression from acute to chronic disease is inversely proportional to age at the time of infection. Among infants and children who become infected between the ages of 1 to 5 years of age, 30-50 percent of them develop a chronic infection, while in adults only five percent of initial infections result in chronic infections.[4] HBV is estimated to be globally responsible for 30 percent of cirrhosis and 53 percent of hepatocellular carcinoma (HCC).[5] An estimated annual all-cause mortality from HBV related infection is 600,000.[6]

In South-East Asia, China, most parts of Africa, Pacific Islands, and some parts of the Middle East, the prevalence of HBV is high (8-15%), and it is in these areas where almost 45 percent of global cases of HBV infected individuals reside. In South Asia, Russia, Eastern and Southern Europe, Central and South America the prevalence of HBV is intermediate (2-7%) with almost forty three percent of all global infections. While the remaining global twelve percent of HBV infections pertain to the low prevalence countries of Western Europe, Australia and the United States (Fig. 2.15.1).[7,8]

Prevalence in India

Several studies from different parts of India showed different levels of prevalence. Based upon systematic review and meta-analysis of published studies, it was found that the mean HBV prevalence in non-tribal population is 2.4 percent while in tribal population it was 15.9 percent.[9] According to WHO, HBV prevalence in India among the general population ranges from 0.1 to 11.7 percent, while most other studies find the prevalence to be between 2 to 8 percent.[10] With an average HBV carrier rate of 5 percent, the estimated total number of HBV infected individuals in India is 50 million or 15 percent of the entire HBV pool of carriers in the world.[10] Gender differences also exist since males are more frequently infected than females.[4]

Genotypes

HBV is composed of eight genotypes, A to H, with distinctive geographic distribution. Genotype A is more prevalent in India, North America and Northwestern Europe and in some parts of South America. However, genotypes B and C are found mostly in Asia, while genotype D is found mostly in the Mediterranean region and Eastern Europe. Likewise, genotype E is specific to Western Africa, and genotype F is found in South America. Genotype G is reported in France, Germany, the United States, Mexico and Central America while genotype H in Central America.[11-17]

Differential treatment response and prognosis also characterize each genotype: genotype A and B have better

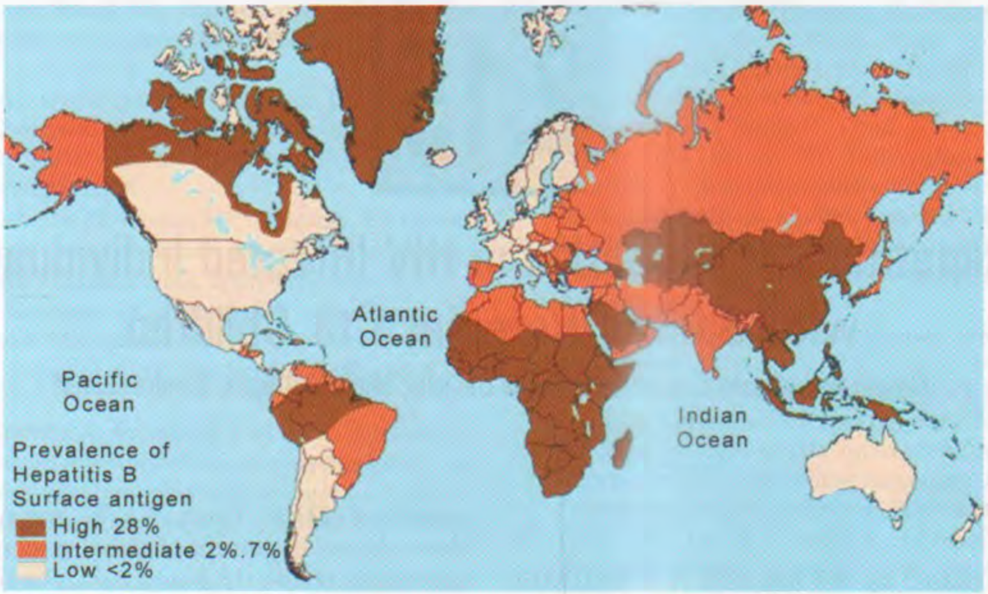


Fig. 2.15.1: Prevalence of chronic HBV infection, 2006.[18]

(Data from Center for Disease Control. Travelers' health: yellow book. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2008. Available at: http://wwwn.cdc.gov/travel/yellowBookCh4-HepB.aspx#363. Accessed February 15, 2010)

response to interferon treatment, compared to those with genotype C and D. Among young patients in India, genotype D is associated with more severe liver disease and HCC than genotype A.[4]

HIV and HBV Co-infection

Worldwide approximately 10 percent of HIV patients are co-infected with HBV.[19] With a 350 million global prevalence of HBV and 40 million HIV prevalence, the estimated prevalence of HBV/HIV is around 2 to 4 million individuals. HBV infection in HIV positive patients ranges from 6 percent to 14 percent in Unites States and Western Europe. Among high-risk groups, HBV/HIV co-infection rates are 9 to 17 percent in men having sex with men, 7 to 10 percent in injection drug users and 4 to 6 percent in heterosexuals.[20] The co-infection rates of infection vary among different parts of the world and are the highest in Asia and Sub-Saharan Africa.[21]

The incidence of acute hepatitis B in children in the United States (under 19 years) has decreased from 13.8 cases per 100,000 population (10 to 19 years) in the 1980s to 0.34 cases per 100,000 population in 2002. The more profound reduction in children under 15 years of age (0.03 cases per 100,000 population) was primarily due to successful universal hepatitis B vaccination of infants since 1991.[22, 23]

In India, HBV/HIV co-infection rates vary according to the region of the country. In Chennai, South India it was reported to be 6 percent, 7.5 percent in Chandigarh, Northwest India, and 16 percent in Mumbai, and Western India.[24] A sero-prevalence study of viral co-infections among pediatric populations performed in North India found that 30 percent of children tested positive for HBsAg among 101 HIV positive children and 27 percent tested positive for HCV, while 10 percent tested positive for both HBV and HCV.[25]

Transmission

The three major routes of transmission for HIV, sexual, parenteral and vertical transmission, are also routes for HBV transmission. Unlike HIV, HBV can survive outside the body for at least 7 days. During that time the virus is still infectious and can potentially infect a non-exposed person. In 2005, high-risk sexual activity or injection drug use was associated with 79 percent of new HBV infections.[20]

Settings likely to be involved in transmission of HBV include:

- Sharing injection needles by illicit drug users
- Unprotected sex with infected partner
- Occupational/workplace exposures to potentially infected human blood or body fluids
- Transfusion of unscreened blood or blood products
- Medical procedures with contaminated needles or equipment
- Direct skin contact with infected wound exudates by patients with open skin lesions (scratches, scabies, impetigo, etc.).

Modes of transmission most frequently found in developing countries (e.g. India) include:

- Mother-to-child or perinatal transmission
- Early childhood exposure with infected household contacts
- Blood transfusions
- Unsafe injection practices
- Unsafe sexual contact

Perinatal transmission of hepatitis B is efficient, especially among women who are HBeAg positive, with most of the transmission occurring at the time of labor and delivery. Most other pediatric cases (excluding sexual transmission among teenagers and pre-pubescents) occur through household percutaneous exposure.

Clinical Presentation and Natural History

The incubation period for HBV infection is 90 days on an average (range: 30-180 days). HBV can cause acute illness which may persist and lead directly to chronic illness. The spectrum of HBV disease includes: acute infection, chronic infection, cirrhosis and hepatocellular carcinoma (HCC). The clinical stages are defined by characteristic findings of biomarkers in serological testing especially hepatitis B antigens and antibodies (Table 2.15.1).

Acute HBV Infection

The diagnosis of acute infection is made when HBsAg, anti-HBc, and IgM anti-HBc are positive and anti-HBs is negative (Table 2.15.2). Clinical presentations in children can range from asymptomatic to fulminant hepatitis. Children over 5 years old, who are symptomatic have presentations similar to adults, but children under 5 years and immunosuppressed adults are usually asymptomatic. Illness typically begins 2-3 months after HBV exposure (range: 6 weeks-6 months). A serum sickness-like syndrome may be followed by constitutional symptoms like fatigue, nausea, abdominal pain and low grade fever. On physical examination the patient may have jaundice and tender hepatosplenomegaly. Acute illness may last 2-4 months. Patients above 60 years of age may have a severe disease presentation with case *fatality* of about 1 percent.[27] Primary HBV infection is self-limited in most of the patients and elimination of virus from blood renders lifelong immunity. However, in a small percentage of cases, it may progress to chronic infection with continued *viremia*. This patient may develop cirrhosis or HCC. The risk of progression to chronic disease is highest in neonates (90%), about 25 to 50 percent in children between ages 1 to 5 years, and less than 5 percent in older children and adults[27] (Fig. 2.15.2).

Upon HBV infection, viral and immune markers are detectable in the serum within one month. The first detectable marker is HBsAg, followed by HBeAg and HBV DNA. Titers may be elevated during incubation, but start decreasing once symptoms manifest and may be undetectable during the peak clinical period.[30] Antibody to core antigen (anti-HBc) is detectable with the onset of clinical symptoms, but core antigen itself does not appear in the blood. The IgM type of immunoglobulin is used in the diagnosis of acute infection. Before advanced diagnostic tests were available, IgM antibody was the only marker detectable in the window period (the time between the disappearance of HBsAg and the appearance of anti-HBs).

Patients who clear the virus become negative for HBsAg and positive for anti-HBcAb, which is associated with long lasting immunity (Fig. 2.15.3). The presence of anti-HBsAb and anti-HBcAb (IgG) is indicative of recovery and immunity from a natural HBV infection while presence of only anti-HBsAb is indicative of a successful vaccine response. Few patients who develop chronic infection have persistently positive HBsAg and anti-HBc (IgG) for more than six months (Fig.2.15.4).

Presence of HbeAg correlates with active viral replication, high viral load and infectivity. This antigen is synthesized from an area on the DNA preceding the area that codes for core antigen.[31] Any mutations in this area

Table 2.15.1. Common serological markers of HBV infection[26]

Marker	Explanation	Diagnostic use
HBsAg	Hepatitis B surface antigen	Protein on the surface of HBV First serologic marker to appear. Persistence for more than 6 months suggests chronic HBV infection
Anti-HBs	HBsAg antibody	Neutralizing antibody. Indicates recovery and/or immunity to HBV the only marker detectable after immunity conferred by HBV immunization
HB eAg	Hepatitis B e antigen	Indicates active replication of HBV and high-risk of transmission
Anti-HBe	Antibody to Hepatitis B e antigen	Less active HBV replication. Decrease of HBV infectivity and remission of disease
IgM anti-HBc	IgM Antibody to Hepatitis B core antigen	Indicates recent infection with HBV ≤6 months. Presence with high index value during acute HBV infection and usually disappears within 6 months
IgG anti-HBc	IgG Antibody to Hepatitis B core antigen	Not a neutralizing antibody and presence indicates an exposure to HBV

Table 2.15.2. Interpretation of Hepatitis B Serologic Test Results[28]

Tests	*Results*	*Interpretation*
HBsAg Anti-HBc Anti-HBs	Negative Negative Negative	Susceptible
HBsAg Anti-HBc Anti-HBs	Negative Positive Positive	Immune due to natural infection
HBsAg Anti-HBc Anti-HBs	Negative Negative Positive	Immune due to Hepatitis B vaccination
HBsAg Anti-HBc IgM anti-HBc Anti-HBs	Positive Positive Positive Negative	Acutely infected
HBsAg Anti-HBc IgM anti-HBc Anti-HBs	Positive Positive Negative Negative	Chronically infected
HBsAg Anti-HBc Anti-HBs	Negative Positive Negative	Interpretation unclear; four possibilities: 1. Resolved infection (most common) 2. False-positive anti-HBc, thus susceptible 3. Low level chronic infection 4. Resolving acute infection

Adapted from: A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. Part I: Immunization of Infants, Children, and Adolescents. MMWR 2005:54(No. RR-16).[28] *http://www.cdc.gov/hepatitis/HBV/Testing Chronic.htm # section3*

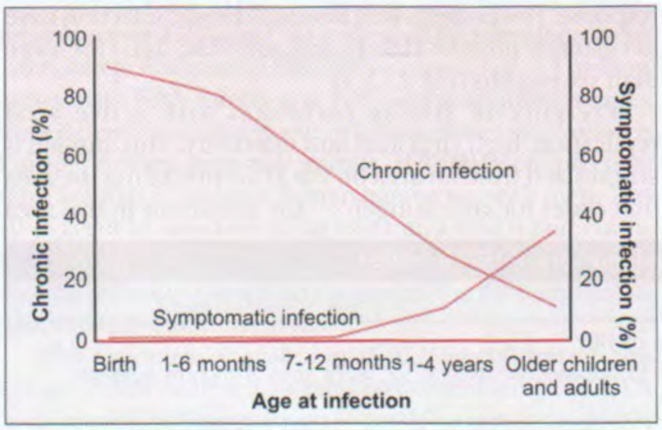


Fig. 2.15.2: Outcome of HBV infection by age at infection

Source: Adapted from Asian Liver Center at Stanford University[29]

can cause failure of production of HBeAg. These viruses are called precore mutants. The presence of a core or precore mutant leads to an HBeAg negative chronic hepatitis, with an associated higher-risk of development of cirrhosis.

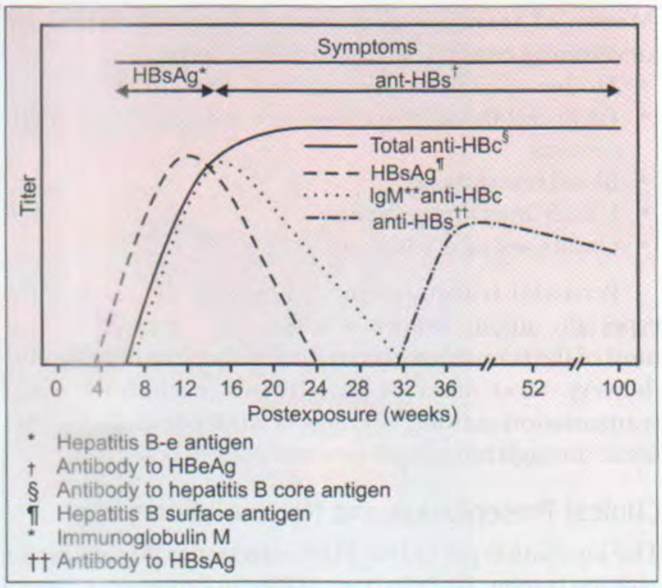


Fig. 2.15.3. Typical Serologic course of acute hepatitis B virus infection with recovery.[27]

Source: MMWR, 2008. 57 (RR08)[27]

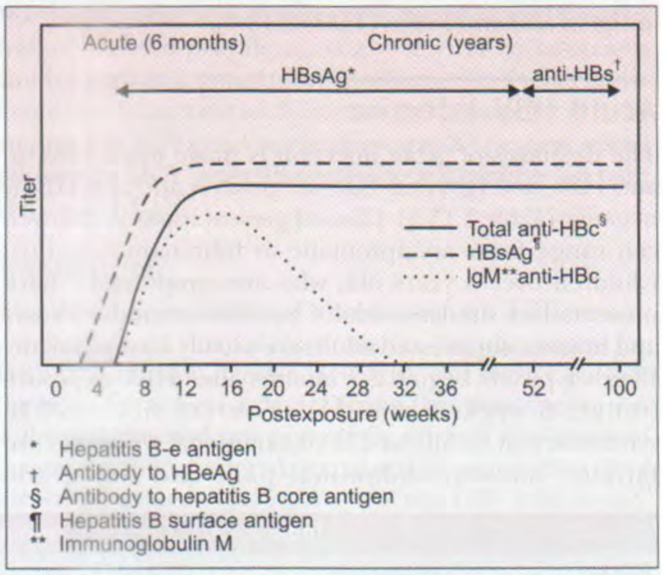


Fig 2.15.4: Typical Serologic course of acute hepatitis B virus infection with progression to chronic HBV.[27]

Source: MMWR, 2008. 57 (RR08)[27]

Chronic HBV Infection

The diagnosis of chronic HBV is made when HBsAg and anti-HBc are positive on two separate samples tested six months apart or when HBsAg and anti-HBc are positive and IgM anti-HBc is negative on a single sample. The majority of children with chronic HBV remain

asymptomatic and develop normally. Some children may have extrahepatic manifestations like glomerulonephropathy, both membranous nephropathy and, less often, membrano proliferative glomerulonephritis.

The natural history of chronic HBV infection in children is variable. It depends upon various factors like age, route of infection and ethnicity. Children from countries where HBV is endemic are more likely to acquire perinatal infection with high levels of viral replication and positive HBeAg,[32, 33] whereas children from non-endemic countries usually clear HBV viral DNA and HBeAg by second decade of life.[34] The symptoms, progression and development of chronic infection are related to the age at the time of infection. Most perinatal and early childhood HBV infections are asymptomatic, with typical illness (consisting of nausea, vomiting, abdominal pain, fever, jaundice, choluria) occurring in 5-15 percent of children 1-5 years old and 33-50 percent of older children or adolescents. Those with perinatal infection might have normal LFTs and minimal histologic changes despite elevated HBV DNA for many years after initial infection. The risk of progression to chronic infection is >90 percent in infected infants, 25-50 percent in children infected between ages 1-5, 6-10 percent in older children and adults. Immuno compromised individuals are at higher risk of developing chronic infection. 25 percent of children with chronic HBV infection will develop hepatocellular carcinoma or cirrhosis.[27] Infants with perinatal infection are also less likely to have HBeAg seroconversion; by age 10, only 1/3 of them will clear HBeAg. Although children with infection at a later age have more active disease, they are more likely to clear HBeAg. Intensity of fibrosis and liver injury varies and is proportional to age at infection and ALT activity.

Chronic HBV infection generally develops over many years and is divided into three major phases: Immune tolerant, immune active and inactive carrier phase (Table 2.15.3 and Fig. 2.15.5)

The immune tolerant phase occurs in almost all infants and children who are perinatally infected. They have active viral replication with little or no disease activity characterized by high viral DNA levels, normal ALT, positive HBeAg and negative anti-HBe. Liver biopsy is usually within normal limits. This phase lasts several decades in perinatally infected children.

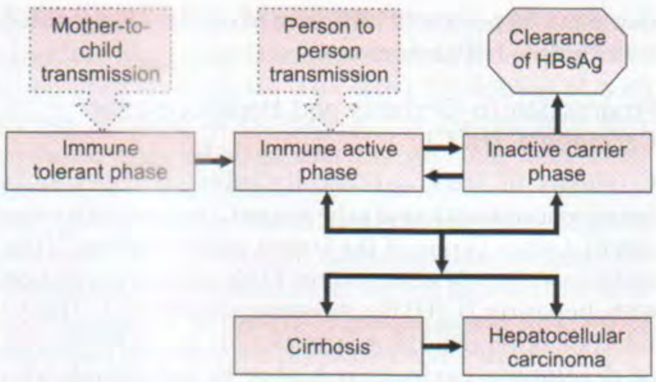


Fig. 2.15.5: Natural history of chronic HBV infection

Source: NIH Consensus Development Conference Statement: Management of Hepatitis B.[37]

Most of the infected children and adults ultimately progress to the immune active phase. During this phase there is inflammation of the liver and elevated liver enzymes. HBV DNA is persistently high with either HBeAg positive and anti-HBe negative or Anti-HBe positive and HBeAg negative (Table 2.15.3).

As they start clearing HBeAg and develop anti-HBe, most patients enter into a third inactive carrier phase. During this phase, ALT returns to normal with low or undetectable HBV DNA. Liver biopsy will show some inflammation with no or minimal fibrosis. Patients in this phase are at lower-risk of HCC. However, many patients from inactive carrier phase can transition back to immune active phase leading to chronic active disease (Fig. 2.15.5). The rate of this seroconversion from HBeAg to anti-HBe is 5-20 percent per year. This is typically associated with decline in HBV DNA levels. However, some individuals with precore and core mutants that disrupt HBeAg production, are able to prod uce high levels of HBV DNA.[36] These mutations are common in Southeast Asia and southern Europe.

A very small percentage of patients may clear HBsAg and develop anti-HBs and are considered to have cleared HBV infection, evolving into "latent" hepatitis B. The natural history of this condition is not well understood, however, they are unlikely to have progression of liver disease. The World Health Organization (WHO) estimates

Table 2.15.3: Phases of chronic HBV infection

Phases of chronic HBV	*Immune tolerant*	*Immune active*		*Inactive carrier*
HBe Ag Anti-HBe	Positive Negative	Positive Negative	Negative Positive	Negative Positive
ALT	Normal	Elevated		Normal
HBV DNA	> 2 x 10^3 - 10^7	> 2 x 10^3-10^7		< 2 x 10^3-10^7
Liver Histology	Normal/Minimal Inflammation	Chronic Inflammation		Inflammation, no or minimal fibrosis

Adapted from WHO, Management of Hepatitis B and HIV co-infection, clinical protocol for WHO European Region.[35]

that about 90 percent of HBV related deaths are associated with chronic HBV infection.

Progression to Cirrhosis and Hepatocellular Carcinoma (HCC)

Cirrhosis in HBV chronically infected children is infrequent and was found to be around 3 percent with mean age of 4 years in one of the largest cohort studies.[38] The children with cirrhosis were more likely to have co-infection with hepatitis D (HDV) infection, hepatitis C (HCV) infection or received blood transfusion. In adults, the risk of developing cirrhosis is higher in individuals who acquired infection perinatally and those who abused alcohol. HCC is described in both children and adults with chronic HBV. HBV is responsible for 60-80 percent of liver cancers worldwide and is the leading cause of HCC, the most common type of primary liver cancer. Individuals with chronic HBV infection are at 200-fold increased risk of developing liver cancer than those who are not infected.[29] The risk factors for developing HCC are duration of infection, degree of histologic injury, levels of HBV DNA, co-infection with other viruses like HCV and HIV and presence of cirrhosis. The risk is also higher in those patients with positive HBeAg, compared those with presence of HBsAg and negative HBeAg (except for those with core mutants). In children, HCC was associated with HBV genotype B while in young adults it was associated with genotype A.[39]

Effect of HIV Infection on HBV Disease Progression

HBV infection is more severe in HIV infected individuals. HIV HBV co-infected patients have significantly elevated HBV DNA levels and HBeAg. They are less likely to clear HBV DNA or lose HBeAg.[20] The higher HBV replication leads to more severe liver disease and an increased risk of cirrhosis. The cirrhosis and HCC appear to be more aggressive and occur at an earlier age than those in non-HIV patients.[19] The risk of reactivation of HBV is higher in HIV patients, as is the risk of liver-related mortality.

Effect of HBV infection on HIV Disease Progression

In contrast to HIV causing severe HBV infection, HBV has not shown to have any significant effect on HIV pathogenesis and disease progression. However, it is found that there is an increased risk for liver related mortality in co-infected patients and risk of increased hepatotoxicity in those undergoing retroviral therapy.

Management of Hep B and HIV

The ultimate goal of treatment management of hepatitis B (HBV) infection is the ultimate reduction of the morbidity and mortality related to liver disease. A variety of end points has traditionally been used to signal successful treatment of HBV infection, such as the normalization of serum aminotransferases, the decrease or undetectability of HBV DNA viral load, improvement of hepatic histology, and, clearance of HBeAg with and without anti-HBe antibody. Liver cirrhosis proper is most frequently prevented by suppression of HBV DNA viral load and seroconversion to anti-Hbe. Specific treatment with nucleotide/side agents is effective for an indefinite period of time (or until resistance develops) in patients who fail to seroconvert, or are HBeAg negative. Once successful treatment is achieved, it is continued for six to twelve months after seroconversion is detected.

The crucial decision in the treatment of HBV infection is the timing of treatment initation. The current recommendations for initiating treatment include: Demonstrable active viral replication defined as an HBV DNA of >20,000 IU/ml and presence of HBeAg, or HBV DNA of >2,000 with absence of HBeAg, biopsy depicting at least moderate-to-severe necroinflammation, and an elevation of serum aminotransferases greater than twice the upper limit of normal levels.

In general, acute Hepatitis B infection does not warrant antiviral treatment, but only supportive care. In HIV coinfection, if the patient requires HIV therapy, HBV treatment should be pursued notwithstanding the stage of hepatitis. And in those cases when HIV therapy is not indicated, only those medications active against HBV (and not HIV) are recommended, i.e. telbivudine, adefovir and pegylated interferon alpha. These agents, when used as HBV monotherapy can have specific clinical impact; telbivudine, for example, causes higher rates of HBV resistance and similarly, adefovir resistance in turn decreases sensitivity to tenofovir which can be potentiated by pre-existing lamivudine resistance.

Lamivudine, emtricitabine and tenofovir disoproxil fumarate can be used in the coinfected patient, for treatment of both the HIV and HBV agents. Since, the efficacy of these nucleosides (lamivudine, telbivudine, entecavir) and nucleotides (adefovir, tenofovir) is not compromised by HIV coinfection, they are considered to be of utmost benefit. Moreover, there is no cross-resistance between nucleosides and nucleotides, and, therefore, they can be used in combinations (e.g. lamivudine with adefovir or tenofovir with emtricitabine). This combination therapy would not necessarily increase the potency of the regimen, but it may delay the emergence of HBV resistance. It is worth noting in this context that tenofovir and emtricitabine are the backbones of HIV therapy.

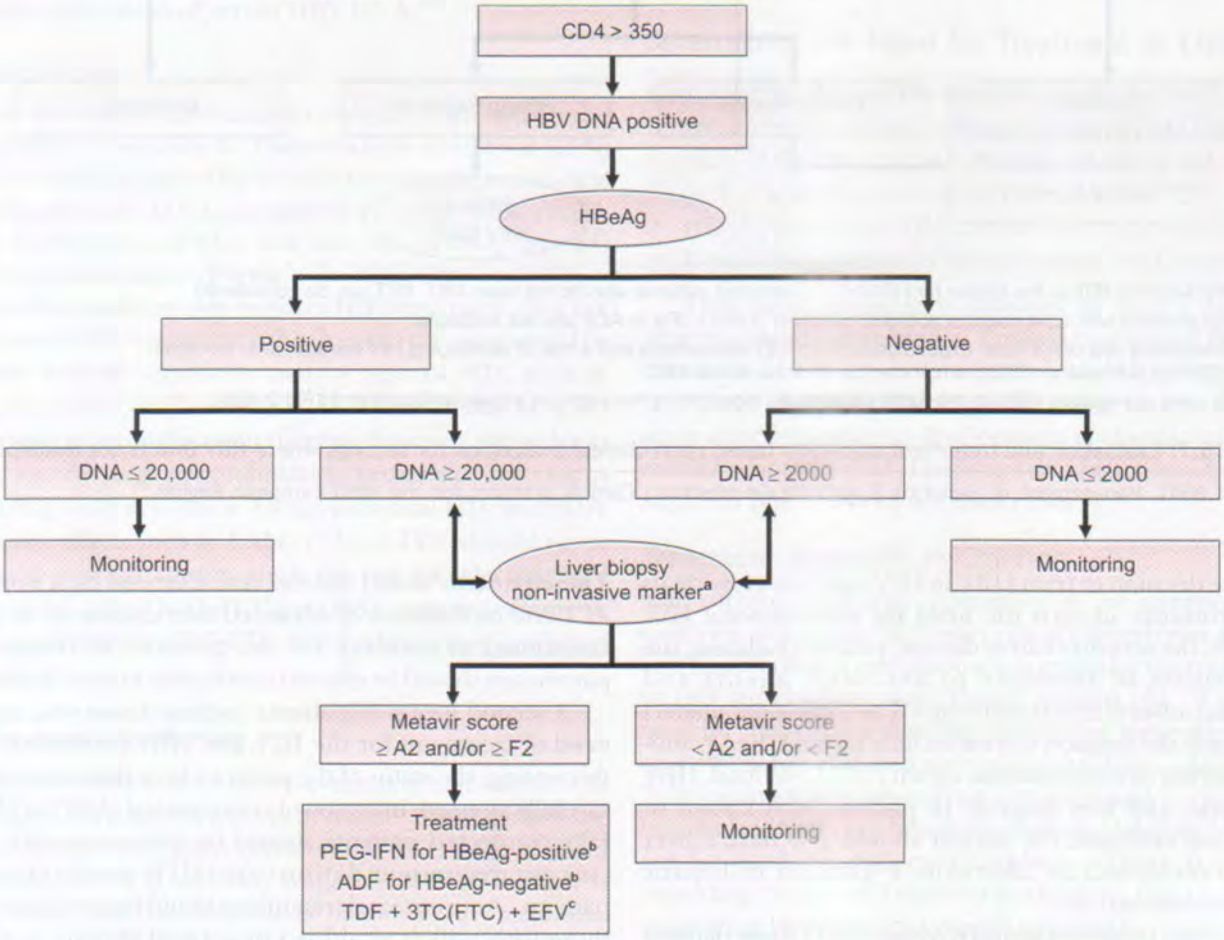
In the event that HBV resistance emerges, addition of another agent (e.g. tenofovir to lamivudine) is preferred over substitutions. It is worth noting, that lamivudine resistance as (when used as monotherapy) in coinfected

patients can develop more swiftly than in HBV monoinfected patients. Similarly, HBV resistance to lamivudine is more commonly found among HIV coinfected patients, and therefore tenofovir should be coupled with lamivudine whenever this agent alone is considered. Analogously, the addition of tenofovir to lamivudine is preferred over "switching" to tenofovir from adefovir, since it will defray eventual tenofovir resistance to HBV. Entecavir should be avoided in the setting of HIV infection, since it can select for lamivudine resistance (through an M184V mutation).

The treatment logistics of both infections are not analogous. The mode of action of the agents used in each viral infection is quite distinct, the anti-HBV medications target the same segment of the HBV life-cycle, while the anti-HIV medications target the virus at various stages of its replication.

In general, patients with HIV infection and HBV infection are more likely to develop chronic hepatitis B disease and have increased HBV DNA levels. They are also more likely to be HBeAg positive and are more likely to progress to cirrhosis. The active replication of both viruses leads to an increase in the risk of both liver cirrhosis, and end stage liver disease, and, more easily devolve to hepatocellular carcinoma. Finally, based on both known drug resistance patterns and the synergistic morbidity of co-infection, early initiation of anti-HIV therapy is recommended in coinfected patients to enable optimal control of the HIV replication and stave off or decelerate the otherwise relentless hepatic destruction.

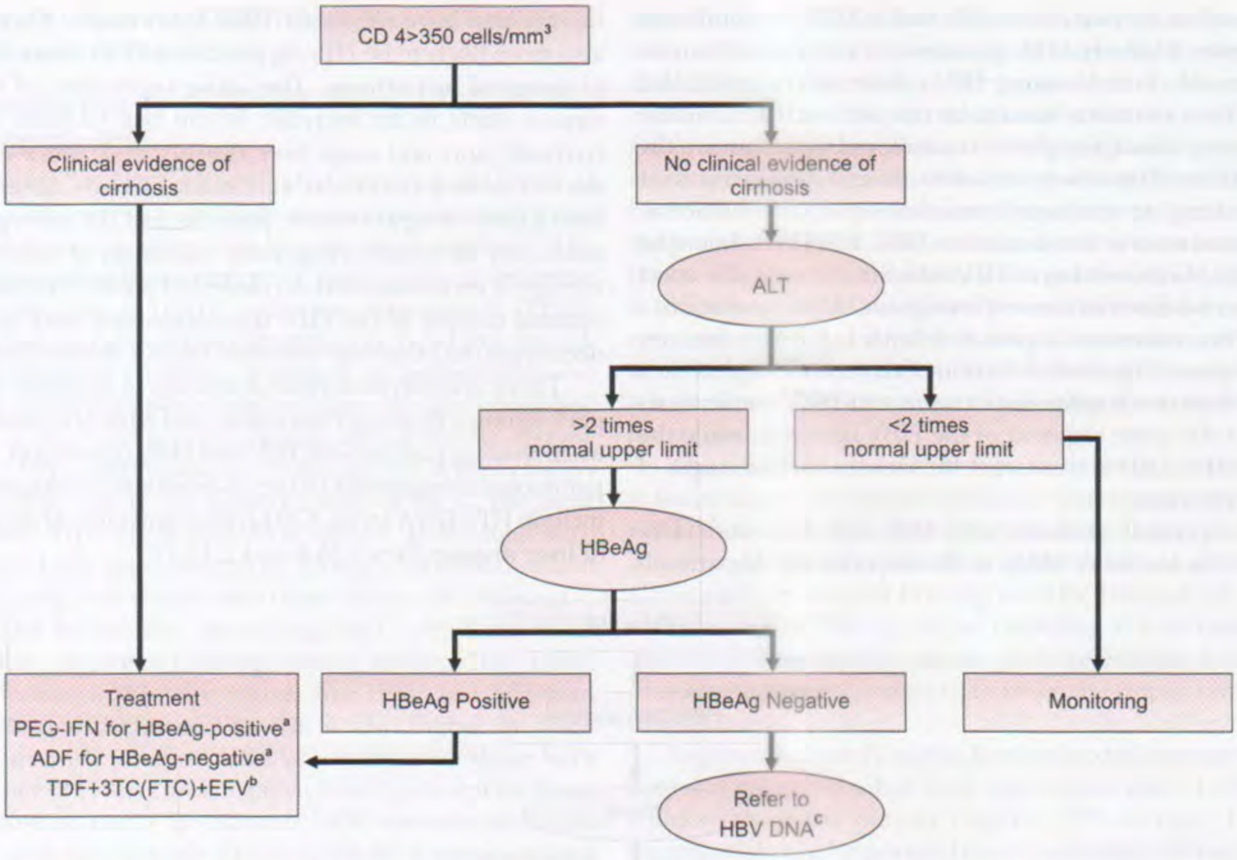
There are different clinical settings to consider after performing a thorough laboratory and clinical evaluation when treating patients with HIV and HBV coinfection. The paramount components of the co-infection investigations include HIV DNA levels, CD4 count, and clinical severity of liver disease (Figs 2.15.6 and 2.15.7).[35]



[a] Non-invasive markers: Fibro test-serum markers, Fibro scan-image technique.
[b] Either PEG-IFN or ADF is the choice for HBV/HIV-co infected patients who do not need ART. ART can be considered for patients with CD4 count of 350-500 cells/mm^3 if PEG- IFN or ADF are not available.
[c] Premature use of ART can expose patients to ART side-effects and a risk of developing HIV resistance to tenofovir (TDF) or lamivudine (3TC), which can compromise future ART.

Fig. 2.15.6: Evaluation and treatment algorithm-based upon determination of HBV DNA and absence of clinical cirrhosis.[35]

Source: WHO. Management of Hepatitis B and HIV Co-infection: Clinical protocol for the WHO European Region.[35]



[a] PEG-IFN or ADF is the choice for HBV/HIV co-infected patients who do not need ART. ART can be considered for patients with CD4 count of 350-500 cells/mm^3 if PEG- IFN or ADF are not available.
[b] Premature use of ART can expose patients to ART side-effects and a risk of developing HIV resistance to tenofovir (TDF) or lamivudine (3TC), which can compromise future ART.
[c] In case of negative HBeAg, the further diagnostic algorithm is the same as shown in Algorithm 1:(Fig 2.15.6).

Fig. 2.15.7: Evaluation and treatment algorithm based upon clinical evaluation for settings where HBV DNA is not available.[35]

Source: WHO. Management of Hepatitis B and HIV Co-infection: Clinical protocol for the WHO European Region.[35]

The decision to treat HBV in HIV infected individuals must consider in turn the need for antiretroviral HIV therapy, the severity of liver disease, patient readiness, the predicition of response to anti-HBV agents and potential adverse effects of therapy. The clinical parameters that guide the decision to treat include serum HBeAg, anti-HBe, serum delta antibodies, serum HBV DNA load, HBV genotype, and liver staging. In patients with known or suspected cirrhosis, the patient should also have a liver sonogram as well as laboratory evaluation of hepatic transaminase activity.

The first treatment group is comprised of those patients that do not require treatment for either infection. In general, these are patients with stable HIV disease in the setting of no clinically significant liver disease. These patients should have a CD4 count of > 350 cells/mm^3, mild HBV disease (HBV DNA <20 000 in HBeAg-positive patients, or HBV DNA <2000 in HBeAg-negative patients). These patients would also be characterized by a normal ALT and no evidence of advanced liver disease on biopsy. Continued monitoring for the presence of treatment parameters should be effected indefinitely in these patients.

A second group of patients include those who are in need of treatment for the HIV and HBV coinfection. In this setting, the status of the patient's liver disease must be carefully assessed. Initiation of antiretroviral (ART) in HBV/HIV coinfected patients should be consonant with the current recommendations for HIV monoinfected patients. Antiretroviral treatment should be considered in those with a high viral load or a rapid decline in CD4 count, and should be initiated before the CD4 count falls to less than 200 cells/mm^3.

In patients with CD4 count of 200-350 cells/mm^3, the decision to treat the HBV should be based upon the clinical status of the patient as well as the evaluation of HBV DNA levels.

In the HBeAg-positive patients with HBV DNA >20 000 IU/ml and HBeAg-negative patients with HBV DNA >2000 IU/ml, the ART regimen must include two dual-activity drugs (anti-HBV and anti-HIV).[35]

However, in patients with low levels of HBV DNA, an ART regimen containing two dual-activity drugs is optional, but highly recommended. In this clinical setting, there is a high risk of immune reconstitution and reactivation of the HBV. For patients with more advanced HIV disease and CD4 counts <200 cells/mm^3, due to the risk of immune reconstitution, the inclusion of two dual-activity drugs is highly warranted.[35]

Goals of Treatment

HBV treatment goals are the same for individuals with and without HIV co-infection. These clinical objectives include alanine aminotransferase (ALT) normalization, HBeAg seroconversion, improvement in liver histology and sustained suppression of serum HBV DNA.[40]

Medications

There are several medications currently approved for the treatment of hepatitis B. These include interferon (IFN, the first drug approved for chronic hepatitis B), lamuvidine (LAM), adefovir (ADV), entecavir (ETV), telbivudine (LdT), and emtricitabine (FTC). The selection of drug depends on the *aforementioned* criteria.

In the candidate that requires HBV treatment, (but not necessarily HIV treatment), the drugs to consider would be agents without significant activity against HIV, such as pegylated IFN, LdT, or ADV.[2] ADV or LdT may be good alternatives as single agent therapy; however, these drugs may also be used in combination because of the risk of selecting drug resistance. Drugs with dual HIV and HBV antiviral effect, such as LAM, FTC or TDF should never be used as single agents, given the risk for selecting HIV resistance. When both HIV and HBV require treatment, the combination TDF-FTC (or LAM) is the preferred choice.[40]

Treatment Monitoring

Several variables must be re-evaluated and monitored throughout a patient's treatment course. These include the monitoring of liver function studies, HBV DNA levels, and serum hepatitis B antibody response. If ART therapy is employed, CD4 counts should be obtained every 3 months. In addition, HIV viral load levels should also be monitored every 6 months. The patient should be monitored for respective side effects of the drugs used in their treatment course. The clinician should be vigilant for signs of hepatotoxicity and recognize that decompensated liver cirrhosis is a contraindication for further aggressive management.

Prevention of Hepatitis B in HIV Exposed or Infected Children

Prevention of perinatal infection in exposed or infected children is of crucial importance, due to the efficacy of the currently available drugs. Hepatitis B vaccination is 90-100 percent effective in preventing perinatal infection. Children whose mothers are infected with hepatitis B should receive both hepatitis B vaccination at birth and hepatitis B immunoglobulin.

Infants and children infected with HIV are less likely than their non-HIV positive counterparts to respond to hepatitis B vaccination. It is for this reason that post-vaccination testing 1-2 months after the last dose is important. If there is no evidence of immunity, a revaccination series should be offered. Individuals that do not respond to a second series are unlikely to respond to further vaccination and should be tested for possible hepatitis B infection.

Determining the Need for Treatment in Children

Criteria that suggest the need for treatment include:

- Documented chronic infection (presence of HBsAg or HBV DNA) for at least 6 months
- ALT at least twice above the normal value
- HBeAg positive or DNA above 10,000 copies
- If available, severity of inflammation and fibrosis.

Treatment response is assessed at least 6 months after completion of treatment. Target is clearance of HBeAg, clearance of HBsAg, normalization of ALT, decrease in DNA and improved histology. Treatment at the time of acute infection, prior to development of chronic infection remains controversial. The long-term benefits of treating hepatitis B in children are not known.

Treatment Regimens in Children

The current treatment regimens that are approved for children older than two years old are interferon alfa-2a and Lamivudine. Emtricitabine is licensed for the treatment of HIV for children older than 3 months old. It can be used for the treatment of hepatitis B, but currently is not approved for this indication in children. Adefovir, Telbivudine and Entevavir are not approved in children, but clinical trials are being conducted. Adefovir should not be used in coinfected children. There is debate regarding the use of Tenofovir in children, due to studies suggesting bone loss and growth stunting in monkeys. At this time, a liquid formulation is not available; if used, the dose is similar to that used in adults, approximately 175 mg/m^2.

Interferon alfa-2a is the drug that has been studied the most for treatment of hepatitis B in children. Studies have shown that 35 percent of children treated with this drug

will lose HBeAg (as compared to 11 percent of children on placebo) and 10 percent will lose HBsAg (as compared with 1 percent of children on placebo). Response to treatment also correlates with normalized ALT and improved histology. The long-term benefit of treatment is unknown. Recommended dosing is 5-10 million units/m^2 IM three times a week for 4-6 months. Adverse effects in children are similar to those in adults, and include fever, headaches, myalgia, neutropenia, worsening hepatitis, depression and irritability. A transient decrease in height and weight growth is also a potential side effect of interferon in children but this seems to resolve once therapy is completed. Therapy should be stopped for severe side effects and dose should be temporarily halved for moderate side effects. The dose can then be gradually increased to the full dose.

Interferon *alfa-2a* is mostly recommended in children older than two years, without cirrhosis, with low HBV DNA levels and abnormal LFTs. There are no studies using interferon alfa-2a in HIV positive children, but recommendations for children are similar to those for adults: interferon therapy is the recommended therapy for children who require hepatitis B treatment but do not require initiation on antiretrovirals. Adult studies show that HIV positive individuals are less likely to respond to interferon treatment. Genotypes A and B respond better than genotypes C and D.[41]

Pegylated interferon is used in adults with hepatitis B. It is not currently licensed for use in children.

Pretreatment with steroids is also controversial in the management of hepatitis B but in some studies in Asia, this has been found to be beneficial. However, this strategy has not been studied in coinfected individuals.

Lamivudine at a dose of 4 mg/kg/day is recommended for the treatment of children who are coinfected with hepatitis B and HIV and require antiretroviral therapy. Studies of non-HIV positive children showed virologic response could be obtained in 23 percent of children treated with this drug as compared to 13 percent of children treated with placebo. Dosing for hepatitis B in non-HIV coinfected children is lower (3 mg/kg/day). Unfortunately, the development of HBV resistance to lamiduvine (so-called YMDD mutants) is common with long-term lamivudine monotherapy, especially after 2 years. In adults, combination with tenofovir is recommended to decrease the emergence of resistance.[42]

Prevention

The mainstay of HBV prevention is immunization of all newborns and infants. The routine vaccination schedule includes 3 to 4 doses, first dose given at birth, preferably within 24 hours of birth. Around ninety five percent immunity levels are reached after 3 doses of the vaccine.

Indications for vaccination:

- All new born infants or children and adolescents younger than 18 years old and not previously treated
- High risk groups:
  - Those with high-risk sexual behavior
  - Close contacts of HBV infected persons
  - Injection drug users
  - Hemophiliacs or those requiring frequent blood or blood products
  - Those receiving solid organ transplantation
  - Health care workers and at risk of occupational exposure
  - International travelers to endemic countries
- Doses and schedules
  - Three doses at birth, one and 6 months. The second dose should be given one month after the first dose and third dose two months after the second dose
  - There are 2 dose and 4 dose schedules available based upon type of vaccine used
- Other Prevention Measures
  - Safe sex practices, prevention of drug use, blood safety measure and education to high risk groups and travelers is extremely important in preventing both HBV and HIV.

Case Study

Case 1

Immediately after a natural disaster in a developing country, a 24 years old HIV positive pregnant female arrives at the hospital in labor. She rapidly delivers a live female infant. The woman did not receive prenatal care. Due to the precipitous delivery, there was no time to initiate intravenous zidovudine to the mother. Given the country's precarious and unstable infrastructure, it is impossible to obtain liquid zidovudine for the infant. The mother's hepatitis B status is unknown.

What procedure is recommended in this infant under the circumstances to decrease her risk of developing hepatitis B infection?

Hepatitis B vaccination is recommended and is highly effective in preventing perinatal transmission of hepatitis B. Hepatitis B immunoglobulin could also be considered if the mother were known to be hepatitis B positive.

Unfortunately, you find out that neither the vaccine nor the immunoglobulin is available at this hospital. It takes 2 weeks for the country's road infrastructure to allow transfer of this infant to a tertiary center in the capital city. At this point, an HIV DNA PCR is obtained and is found to be positive. Hepatitis B surface antigen is also detected.

What can you expect to be the natural progression of this infant's hepatitis B?

While infants with perinatal hepatitis B infection are more likely to have asymptomatic disease, they are at greater risk for chronic infection.It is likely that she will be asymptomatic for many years before she shows any evidence of late complications of chronic infection.

Key Messages

- HBV is a DNA virus which causes both acute and chronic liver disease
- It is transmitted via blood, sexual and vertical transmission routes
- Approximately 2 billion infected worldwide with about 350 million with chronic infection and around 600,000 HBV related deaths per year
- Approximately 25 percent of adults with chronic infection later die of liver cancer or cirrhosis
- HBV is 50 to 100 times more infectious than HIV
- HBV is preventable with safe and effective vaccine.

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2.16

Hepatitis C Co-infection in HIV Infected Individuals with Special Reference to Children

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Epidemiology

Hepatitis C Virus (HCV) was only discovered in 1989. It is an enveloped RNA virus. Early rates were grossly underestimated and have been revised as more sophisticated testing methods were developed and increasing number of people tested. In most cases disease is asymptomatic leading to low public awareness and testing. HCV is a major cause of chronic liver disease and is endemic in most parts of the world with estimated overall prevalence of 3 percent. The incidence of HCV on a global scale is not well known due to asymptomatic nature of acute infections. There are estimated more than 170 million HCV chronically infected individuals worldwide.[1,2]

Egypt has the highest prevalence (15 to 20%) of HCV in the world along with high morbidity and mortality from chronic liver disease, cirrhosis and hepatocellular carcinoma (HCC). One of the explanation for this large reservoir of infection in Egypt is past practice of parenteral therapy for schistosomiasis.[3] In Italy, overall prevalence of HCV antibodies is more than 5 percent in some communities with rate of 33.1 percent in those above 60 years. This is attributed to use of glass syringes before 1970 and history of dental therapy.[3] The lowest prevalence of 0.01 to 0.1 percent is reported in the UK and Scandinavia.[4] The patterns of HCV are different in countries with similar rates. For example, the United States, Australia, Turkey, Spain, Italy, and Japan have similar overall prevalence of 1.0 to 1.9 percent but they have different age-specific prevalence. In the United States and Australia, prevalence is highest in 30 to 39 years old and lesser among less than 20 and more than 50 years old indicating infections have spread in the last 20 to 40 years. In contrast, prevalence increases with age in Turkey, Spain, Italy, Japan, and China with majority infections in people above 50 years indicating infections occurred in distant past.[4]

In the United States, prevalence of HCV antibodies is present in approximately 0.2 percent of children ages 6 to 12 and 0.4 percent of those ages 12 to 19. These prevalence rates are similar to the prevalence observed in volunteer adult blood donors.[5] However, prevalence was much higher in high risk groups (50 to 95%) who received blood products for disease conditions like thalassemia or hemophilia before 1990, when no routine screening of HCV was available.[6-8] After routine testing of blood supply was implemented in 1990s, it has almost eliminated this mode as a cause of HCV transmission, especially in western countries. This is changing epidemiology of HCV in developed countries. The prevalence of HCV in children dropped more than 40 percent in late 1990s and almost all the new cases were caused by perinatal transmission.[9] Some of this drop is attributable to blood screening. In addition, programs targeted at mothers and availability of treatment are also contributing to reduction in HCV.

Approximately 3.2 million people in the United States have HCV infection, most of them were likely infected during 1970s and 1980s, when rates were high. In 2007, only 849 confirmed cases of HCV were reported to CDC. However, CDC estimates that there were approximately 17,000 new infections that year.[10] In the United States about one third of young (18 to 30 years) Injection Drug Users (IDUs) are HCV infected. The rate is higher (approximately 70 to 90%) in older IDUs. There are around 5 to 10 million HCV infected individuals in Europe, about 12 million in India and most of them do not know they are infected[11] (Fig. 2.16.1).

Studies have found that 9 to 30 percent of HBsAg-positive individuals are also HCV seropositive.[13] In endemic areas this could be as high as 50 percent.[14]

Prevalence in India

With estimated 12 million HCV carriers, every 15th carrier is an Indian. The burden of HCV has been recognized in recent years in India with advent of HIV epidemic. Prevalent practice of re-using glass syringes by some unscrupulous local medical practitioners, unsafe blood

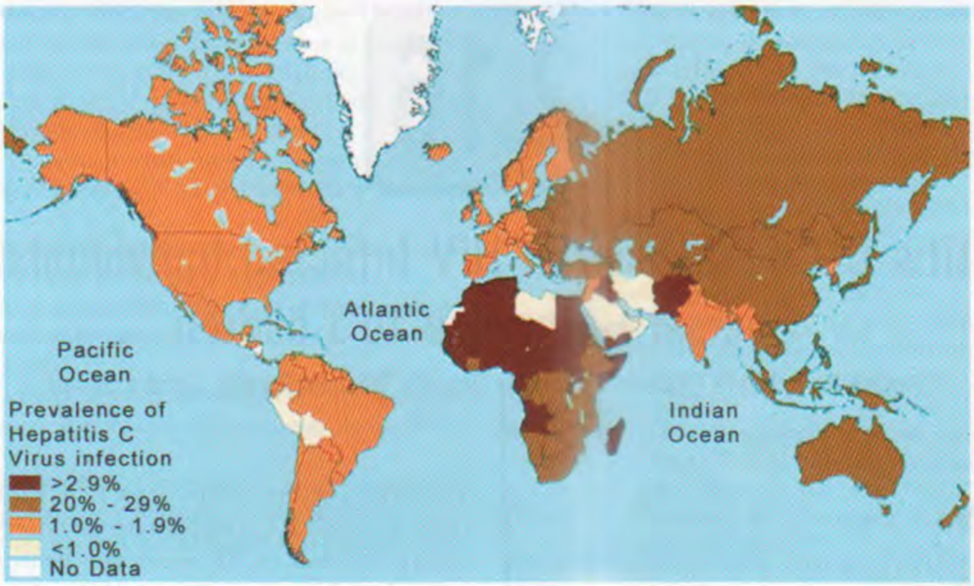


Fig. 2.16.1: Prevalence of chronic HCV infection

Source: WHO, CDC Traveler's Health, Yellow Book http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-5/hepatitis-c.aspx.[12]

banking practices, especially in private sector, and injection drug use in some parts of India, illiteracy and poverty account for HCV spread. There are no systematic large population based studies of HCV epidemiology in India. Population based studies from some states in India found prevalence of HCV in general population to range from 0.3 to 7.78 percent with average of 1.5 percent. Studies based upon data from voluntary or mixed blood donors found average prevalence to be below 2 percent while two studies which studied only professional donors found prevalence of 55.3 and 87.3 percent.[15]

Genotypes

The HCV is classified into 11 genotypes which are identified by a number (1 to 11). There are many subtypes within these eleven genotypes which are identified by a lower case letter) and about 100 strains (numbered 1, 2, 3, etc) based upon genomic sequence.[16]

The genotypes 1 to 3 have a worldwide distribution with types 1a and 1b accounting for 60 percent of global infections. Type 1a is more common in Northern America and Northern Europe while 1b is more common in Eastern and Southern Europe and Japan. Type 3 is predominant in South East Asia including India. Type 5 is mainly found in Middle east, Egypt and central Africa while type 5 is exclusively found in South Africa. Genotypes 6 to 11 are distributed in various countries in Asia.[17-19]

In the United States most common genotype is 1a (about 57%), followed by 1b (about 17%). Genotype 2 and 3 are next common types. The role of genotype on HCV pathogenesis is still controversial but is important for prediction of treatment response to interferon and antiviral drugs. Genotype 1 is more difficult to treat compared to 2 or 3 which have more favorable response to treatment.

HIV and HCV Co-infection

In the United States and Western Europe about 25 to 30 percent of HIV patients are co-infected with HCV and up to 10 percent of all HCV infected patients are co-infected with HIV.[20-22] Worldwide it's estimated that 4 to 5 million individuals are co-infected with HIV and HCV. In certain high-risk groups like IDUs, it may be as high as 80 percent.[20, 21]

HCV is a common infection in HIV infected patients ranging from 10 to 40 percent in different cohorts studied.[23] The routes of transmission are similar to those of HBV and HIV. Children form small percentage of HCV infected population. Most of the infections are caused by exposure to infected blood with perinatal transmission forming a small proportion.

HIV and Hepatitis C Co-infected Children

Children primarily acquire HIV through vertical transmission, with most transmission occurring during the time of delivery. The mother's hepatitis C viral load seems to be associated with higher risk for transmission. Transmission does not seem to be related to the type of delivery and breastfeeding does not increase the risk of transmission of hepatitis C. The risk of mother to child

transmission of hepatitis C is about 2.8-fold higher in women coinfected with HIV. Risk of vertical transmission of HIV also seems to be higher in women who are coinfected with hepatitis C.

Children with HCV infection usually have a more benign clinical course than individuals infected when they are adults and seem to have lower progression, with less rapid development of fibrosis. 90 percent of vertically acquired hepatitis C are asymptomatic, with some mildly elevated ALT levels.

Maternal antibodies passing through the placenta can cause falsely positive anti-HCV antibody in younger infants. For this reason, the anti-HCV antibody is only considered diagnostic of HCV infection in infants older than 18 months. For younger infants, detection of HCV RNA can be used for diagnosis of infection. These tests should be performed after age 1 to 2 months and should be confirmed. Viral RNA can be detected only intermittently.

Transmission

The most common route of transmission of HCV is through direct percutaneous exposure to blood especially when large or multiple. This could be from blood transfusion, transplantations from infected donors or injection drug use. It is less efficiently transmitted in occupational settings with single percutaneous needle stick injury or mucosal exposure to bodily fluids.[24] It can be also transmitted prenatally at birth from an infected mother. The less common routes of transmission are sex with an HCV infected person, sharing personal items with infectious blood like razors or toothbrushes. However, these are very inefficient modes of transmission.[10]

Clinical Presentation and Natural History

Pathogenesis of HIV/HCV Co-infection

Independently, HIV and hepatitis C (HCV) are major global health concerns. Unfortunately, secondary to similar modes of transmission, coinfection with these two viral entities has become increasingly common. There is a growing body of evidence illustrating the synergistic and deleterious effects of this co-infection. Further elucidation of the complex mechanisms underlying the immunopathogenesis of this viral coinfection may facilitate the development of a better knowledge base for future research and novel therapeutic strategies.

There are several observed characteristics of this chronic co-infection. Overall, increased rates of mortality and morbidity have been demonstrated in this co-infected population. These individuals typically have higher rates of HCV viremia, higher levels of HCV RNA, and accelerated progression of liver fibrosis.[25] Several studies from multiple regions have exhibited that this population of patients are at increased risk for end-stage liver disease compared with patients with HCV alone.[26, 27] This accelerated course are likely attributable to the persistence of HCV which depends upon the host's cell-mediated immunity and the activation of the immune system to produce proinflammatory cytokines and fibrosis.[28] The characteristics described above are likely multifactorial and there are several proposed mechanisms to explain the observations described above.

As mentioned above, a concerning feature of HCV and HIV coinfection is the higher risk of accelerated liver disease. Liver fibrosis progression may be related to weak cellular immune responses to HCV antigens in HIV infected patients. HIV infection is characterized by marked decreases of circulating CD4 cells, dysfunction of both CD4 and CD8 cells, and down-regulation of CD28 expression.[29] There are other mechanisms related to the immune response of co-infection which may contribute to increased comorbidity. These include the possibility of altered immune activation associated with HIV disease, altered activation of hepatic stellate cells leading to a modified CD4 and CD8 immune response,[30] and the induction of proinflammatory pathways that may contribute to progression of liver fibrosis.[25]

There is an increasing body of data to suggest that coinfected patients are at higher risk for the development of not only cirrhosis and liver fibrosis, but also of hepatocellular cancer. The development of co-infection at a younger age is associated with shorter survival in HIV/HCV co-infected patients compared with those with HCV infection alone.[31] In addition, studies have also raised the concern that progression from initial HCV infection to Hepato Cellular Carcinoma (HCC) was significantly faster in co-infected patients.[32]

Acute and Chronic HCV Infection

Hepatitis C is very similar to HIV in that once acquired, it primarily results in chronic persistent infection with a high-level viremia. This is related to the fact that extensive antigenic variation occurs, much as occurs with HIV, and anti-HCV antibody cannot confer immunity. Thus, while a given antibody may be neutralizing against a specificed antigenic variant, missions of quasispecies are produced daily and permit immune "escape". In contrast to HIV, however, HCV does not integrate into the host's genome, and so spontaneous or induced remission is achievable. Acute infection is typically clinically inapparent, but may rarely be associated with acute hepatitis symptoms similar to hepatitis B that trigger laboratory testing. Spontaneous clearance of acute infection occurs in approximately 15 percent. The remainder develop chronic hepatitis. Symptoms in this state are typically silent or nonspecific; persistent fatigue may occur, and rarely upon questioning, patients will admit to occasional right upper quadrant ache. Transaminases typically fluctuate around a low mean,

occasionally dipping to normal range. Most often, chronic hepatitis C is diagnosed when transaminases is incidentally detected on routine laboratory evaluation. Chronic hepatitis C may persist for 20 to 30 years, gradually producing fibrosis, before cirrhosis is present. Cirrhosis develops in about 20 percent of chronic hepatitis C cases. HIV co-infection may shorten this interval to 5 or 10 years, perhaps less. Hepatocellular carcinoma affects 20 percent of those with cirrhosis, and those who develop cirrhosis typically decompensate within 5 years. The annual rate of progression to hepatocellular carcinoma is 1 to 7 percent.

Progression to Cirrhosis and Hepatocellular Carcinoma (HCC)

The increased risk of hepatocellular carcinoma (HCC) in patients with hepatitis C infection is well described. The recent increase in the incidence of this malignancy in the Western hemisphere is being attributed to the greater prevalence of hepatitis C in these countries.[33] In the United States alone, it has been estimated that 25 percent of HCC patients have hepatitis C infection.[34] Several other factors serve as prognostic correlates or the adjuvants to this unfortunate devolution in addition to hepatitis C itself, as follows: (a) Coinfection with hepatitis B, (b) Alcohol and tobacco use, (c) Viral genotype 1b, (d) Advanced age and (e) Male gender.[35]

The advent of HCV-related liver cancer often follows two or more decades of infection. Clinical manifestations might include worsening signs and symptoms of cirrhosis such as: jaundice, fatigue and relentless ascites; as well as severe right upper quadrant pain. Other objective data include the alpha-fetoprotein level which is usually elevated, but its rate of false negativity makes it an unsuitable screening tool. In this context, it is worth noting that small HCC may indeed be clinically silent and may only be disproven serendipitously during patient evaluation for liver transplantation.[36]

Finally, definite diagnosis can be effected by liver biopsy which is warranted in the preceding clinical settings and evidence of a sonographic or computed tomography scan hepatic mass.

Effect of HIV Infection on HCV Disease Progression

HIV infection adversely affects all stages of the natural history of hepatitis C infection. HIV infection increases viral persistence following acute hepatitis C infection and rate of hepatitis C viremia. The rate of progression to liver cirrhosis and end-stage liver disease is also enhanced in coinfected patients.[37] Graham and co-workers estimated that superimposed HIV infection increases the risk of liver cirrhosis twofold.[38]

Effect of HCV Infection on HIV Disease Progression

It remains unclear if chronic hepatitis C affects the natural progression of HIV disease. Greub and colleagues showed that coinfected patients had a higher risk of progression to AIDS-defining event or death in patients receiving HAART therapy, even in HIV virologically suppressed patients.[39] Alternatively, Chung and colleagues failed to demonstrate a difference in immune restoration of coinfected patients in a well-controlled AIDS Clinical Trial Group Study.[40] These trials suggest that the effect of HCV infection on HIV disease progression is not significant.

Management of Concomitant HIV and Hepatitis C

Overview

Studies have shown that HIV infection in a person who is also infected with HCV results in higher levels of HCV in the blood, accelerated progression to HCV-related liver disease, and increased risk for cirrhosis and liver cancer. As a result, HCV is now regarded as an opportunistic infection in people with HIV infection, although it is not considered an AIDS-defining illness. The treatment of concomitant hepatitis C and HIV is currently the focus of many recent studies as an enlarging body of literature recognizes the importance of managing this coinfection with evidence based strategies.

Candidates for Treatment

The approach to managing coinfection of hepatitis C and HIV is largely dependent on the status of the patient's hepatitis C and HIV disease activity, stage of liver disease, underlying illnesses, and patient readiness to accept treatment. There are several patient populations to consider when making the decision to initiate treatment. Co-infected patients may require single treatment of hepatitis C or HIV, or both infectious diseases. However, some coinfected patients do not require either treatment, but instead warrant rather close monitoring. We will examine several of these population groups and treatment settings.

One category of patients to consider is that which warrants no treatment. Close monitoring of liver function and HIV status are indicated in patients with CD4 count <350 cells/mm^3 and without evidence of HIV related symptoms or AIDS defining illness. In addition, these patients would not have any evidence of active HCV RNA replication.[41] These criteria are in accordance with the World Health Organization's clinical protocol for management of hepatitis C and HIV coinfection. However, this treatment category is not without controversy. Some

experts have proposed treatment should be initiated for HIV with anti-retroviral therapy (ART) in the setting of coinfection with hepatitis C without consideration of any other clinical data (such as CD4 counts) in order to limit any progression of liver disease alone.[42]

Another clinical scenario would entail those patients who require treatment for hepatitis C alone. This group of patients would have a CD4 count>350 cells / μL and would have no HIV related symptoms or AIDS defining illnesses. This clinical setting is more objectively delineated by HCV genotyping and liver biopsy results. Candidacy for single treatment of hepatitis C in these patients would comprise (a) HCV Genotype 2 or 3, (b) HCV Genotype 1, with viral load ≤ 800,000IU/mL, and (c) HCV Genotype 1 or 4, with viral load >800,000 IU/mL and evidence of moderate to severe portal fibrosis or more severe liver disease.[41, 43]

Analogously, some co-infected patients will require treatment for HIV only. All of these patients would have HCV antibodies but not active HCV RNA viral replication. In this setting, patients can be managed as if they had HIV monoinfection alone and the standard protocol inauguration would be germane.[44] This patient should have a CD4 count of ≤ 350 cells/mm^3 and be symptomatic or, with viral load >100000 copies/mL. In addition, an absolute CD4 count of <200 cells/mm^3 in the absence of symptoms would also warrant HIV monotherapy.

Finally, some patients will require treatment for both hepatitis C and HIV disease. Indications to consider initiation of treatment with ART for HIV are as follows: A CD4 count of <350 in symptomatic patients or in patients with viral load >100,000 copies/mL or CD4 <200. In addition, the patient would have active or chronic liver disease.[41] In most instances the treatment for HIV should be prioritized, especially in patients with advanced AIDS.

When evaluating the patient with HIV and hepatitis C coinfection, the contraindications for therapy must also be considered. However, there are few absolute contraindications to initiating treatment for hepatitis C, such as a history of decompensated cirrhosis (Child-Pugh C) since in these patients, interferon (IFN) therapy is poorly tolerated. In this setting, liver transplantation should always be preferentially considered.[45] Moreover, pregnancy is also a contraindication to initiating therapy for hepatitis C as Ribavirin (RBV) is a potent teratogen. Other considerations pertain to the presence of a mood disorder or other psychiatric conditions, since IFN may lead to an adverse effect with these comorbidities. Cardiopulmonary conditions, as well as alcohol and illicit drug use should also be considered.

The ultimate common goal of treatment in these settings is the achievement of a sustained virologic response (SVR) (defined as undetectable HCV RNA six months following treatment), since it has been associated with decreased progression of liver fibrosis.[45] Furthermore, an SVR is also associated with reductions in liver-related complications and mortality.

Finally, there are various clinical response predictors that have been described, including genotype, baseline viral load, age and underlying comorbidities such as insulin resistance.

Treatment Recommendations

The current standardized treatment for patients with coinfection of hepatitis C and HIV includes pegylated interferon and ribavirin. Multiple clinical trials demonstrate the superiority of pegylated interferon and ribavirin versus standard interferon for the treatment of hepatitis C.[46] Pegylation refers to the addition of a polyethylene molecule to the native interferon which increases its half-life and bioavailability. The recent APRICOT study revealed that the overall SVR rate was 40 percent in the pegylated interferon/ribavirin group compared to 20 percent with pegylated interferon monotherapy and 12 percent with standard interferon/ribavirin therapy.[46] Most trials evaluating the treatment of coinfected patients have involved treating for at least 48 weeks. The dosages and duration of therapy depend primarily on HCV genotype and response to therapy.

Determining the Need for Treatment in Children

Criteria to determine the need for treatment in children are similar to those used in adults. Treatment is recommended for those children with symptomatic infection or advanced histology (bridging necrosis, cirrhosis).

Treatment Regimens in Children

Pediatric treatment recommendations are based on adult data, as there are limited studies in children. Combination therapy with interferon plus ribavirin remains the preferred initial clinical regimen. In children, interferon-alfa remains the main form of treatment. Pegylated interferon can be used, but there is currently not sufficient data in children. Doses of interferon alfa used range from 3 to 5 million units three times a week for 4 to12 months and is preferably combined with ribavirin. Side effects are most commonly influenza-like illness and epistaxis. A transient impairment of height growth can occur, but this resolves when the medication is stopped. Ribavirin can cause hemolytic anemia. A common difficulty with the use of Ribavirin in HIV and HCV coinfected children is that there is a drug interaction between this drug and Didanosine. If Ribavirin is contraindicated, therapy with interferon alone can be attempted.

Patient Monitoring and Side Effects

The significance of reported side effects will depend on the medications employed in the care of the patient. The treating physician must remain vigilant throughout the treatment course. Physicians who treat hepatitis C / HIV co-infected patients should be well-versed with the medication side effect profiles of both ART and hepatitis C drugs and be prompt in recognizing the development of adverse effects. Particular attention should be given to side effects such as rapid or dramatic weight loss, the presence or development of opportunistic infections, HIV RNA suppression, anemia, and neuropsychiatric side effects.

Lab monitoring is essential for patients initiating or continuing treatment for coinfection of hepatitis C and HIV. Platelet count, white blood cell total, and differential count should be reviewed prior to initiating therapy and should be monitored every two weeks for at least the first two months of therapy. In addition, thyroid studies, creatinine, HIV RNA and CD4 counts should be evaluated initially and monitored quarterly. Lipid profile should be evaluated every 6 months. For those female patients of child bearing age, a baseline HCG and monthly HCG testing is warranted. As previously indicated, HCV RNA levels should be assessed at 4 weeks and 12 weeks after the initiation of therapy.

Goals of Treatment

Medications

All four hepatitis C genotypes (1 through 4) are treated on a weekly basis with the same pegylated interferon (PEG IFN) at doses of 180 mg of *alpha-2a* or 1.5 mg per kg of *alpha-2b*. For genotypes 1 and 4, the daily ribavarin dose is 1000 ml for patients weighing less than 75 kg and 1200 mg for patients weighing more than 75 kg. The ribavarin dose for genotypes 2 and 3 is always 800 mg, irrespective of weight. Furthermore, as a rule, genotypes 1 and 4 require a 48-week duration of therapy, while genotypes 2 and 3 require only a 24-week course of treatment. The length of treatment can be tailored to an individual patient based on his initial response to the antiviral therapy.

Prevention

Preventing HCV is extremely important to reduce burden of the disease in the community. Most important is primary prevention which reduces risk of infection in the first place. However, treatment of infected individuals can also prevent spread of HCV.

Some of the preventive strategies include:[24]

- Screening of blood and blood products, and tissues and organs
- Strict infection control practices in health care settings to reduce exposure to needle stick injuries and infected blood and bodily fluids
- Health education and counseling especially of high-risk groups
- Treatment of HCV infected individuals
- Educating Health Professionals
- Continuous surveillance and HCV monitoring.

Case Study

Case 1

Peter, a ten year old boy with a history of hepatitis C and HIV co-infection returns for outpatient follow up. He is on Lopinavir/ritonavir + zidovudine/lamivudine for his HIV infection. His viral load has been undetectable for the past two years on this regimen and his CD4 count is 425. For the past year, his ALT and AST have been mildly elevated. One month ago, his ALT was 84 and his AST 67. On the past visit last month, you requested a liver biopsy. The report shows: "compatible with bridging fibrosis, cannot rule out early cirrhosis"

What further testing would you want to obtain prior to suggesting that Peter be treated for hepatitis C?

- Hepatitis C genotype
- Hepatitis C viral load
- Baseline CBC and TSH

Peter's Hepatitis C Genotype is reported as 1a. His viral load is 5,000.000 copies per ml. His baseline CBC and TSH are normal.

How would you treat Peter's hepatitis C? What is the significance of the genotype (1a)?

You decide to start Peter on interferon alpha 5 million units/m subcutanously 3 times weekly for 48 weeks plus Ribavirin 15 mg/kg/day. Genotype 1 is less likely to respond to therapy than genotypes 2 or 3 (26% vs. 70%), but treatment can still be attempted.

What 3 or 4 key side effects should you monitor for characteristic of drugs – like increased bilirubin or hematuria or splenic abscess? What labs should you obtain periodically and how often?

You instruct Peter's mother to monitor for severe flu-like illness (myalagias, fever, chills, abdominal pain, nausea, vomiting), epistaxis, personality changes and loss of appetite. You order complete cell counts at weeks 2,4 and monthly thereafter. You also order periodic TSH levels.

Peter does develop some fever and malaise after the first dose of Interferon alpha-2b. After this, you recommend premedication with Acetaminophen which decreases this symptom. Upon follow up at week 4, his mother states that he is not eating well. He has lost 2 lb since the initial visit and his family complains that he has become timid and retiring. Due to his complex medical case, he is not attending public school and is being home-schooled by a tutor.

His laboratory results show that he has developed some mild neutropenia (ANC of 1400). You recommend a high-calorie nutritional drink and encourage Peter and his

mother to continue with the therapy. At week 12, re-evaluation of his hepatitis C viral load shows that there is complete virologic suppression. Unfortunately, he has now developed severe neutropenia (ANC 450), so granulocyte colony stimulating factor is initiated Despite these side effects, the family is content with the response to therapy and wish to continue with this. At week 48, Peter's viral load is fully suppressed. Therapy is discontinued. A year later, Peter's hepatitis C viral load remains undetectable. He remains on his HIV antiretroviral therapy and his CD 4 T cell count has increase to 670. He will begin middle school next year.

Key Messages[47]

- HCV is an enveloped RNA virus.
- Estimated 3.2 million people with chronic HCV infection.
- Most efficient route of transmission is large or repeated percutaneous exposure to infected blood, tissue or body fluids.
- Average incubation period is 14 to 180 days.
- 25 to 30 percent of newly infected develop acute symptoms
- 75 to 85 percent develop chronic infection.
- 60 to 70 percent of chronically infected develop chronic liver disease.
- 5 to 20 percent develop cirrhosis over 2 to 3 decades time period.
- Antiviral drugs like ribavarin, and Interferon alpha are used in the treatment.
- There is no vaccine available.

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2.17

Malaria and HIV Infection

Vikram Kumar, Sanjiv Lewin

Malaria is a major public health problem in India. Around 1.5 million confirmed cases are reported annually by the National Vector Borne Disease Control Program (NVBDCP), of which 40-50 percent are due to *Plasmodium falciparum*. India accounts for approximately two-thirds of all confirmed cases reported in the South-East Asia Region. In 2008, 96 million slides were examined, and 1.5 million cases were confirmed from them. The number of cases has fallen from more than 2 million confirmed in 2000 to 1.5 million cases in 2008. Five states account for 60 percent of the cases: Orissa, Chhattisgarh, Madhya Pradesh, Jharkhand and West Bengal. Other highly endemic states include Arunachal Pradesh, Assam, Meghalaya and Tripura.

Malaria HIV co-infection is less known in our setting but there is literature and experiences from Africa, especially in adults. Malaria control is immune-mediated and since HIV infection reduces immunity it is logical to suspect that in HIV infected patients, one would expect an increased incidence of malaria. However, this correlation remains unclear and malaria does not show epidemiological patterns like a typical opportunistic infection in HIV infected persons.

Malaria is caused by intracellular *Plasmodium* protozoa transmitted to humans by female *Anopheles* mosquitoes. Four species of *Plasmodium* cause malaria in humans: *P. falciparum, P. malariae, P. ovale,* and *P. vivax.* Malaria also can be transmitted through blood transfusion, use of contaminated needles, and from a pregnant woman to her fetus. The risk for blood transmission is small but may occur by way of whole blood, packed red blood cells, platelets, leukocytes, and organ transplantation.

The life cycle of *Plasmodium* takes place in both the human host and mosquito vector. The female *Anopheles* mosquito takes a blood meal, during which it injects sporozoites (human infective stage) into the human host. The sporozoites pass through the bloodstream into the liver, where they mature into schizonts that rupture and release merozoites. Some *P. vivax* and *P. ovale* sporozoites remain dormant in the liver as hypnozoites, which may release merozoites into the bloodstream weeks, months, or even years later, causing relapses. After merozoites are released from the liver, they invade red blood cells (RBCs) and during the blood stage mature into trophozoites (ring-form). In the RBCs, trophozoites multiply asexually into schizonts that rupture and release merozoites, which in turn infect more RBCs. As merozoites leave the RBC, the latter is ruptured and destroyed. As thousands of merozoites causes hemolysis, the host becomes progressively anemic. In addition, schizont rupture and merozoite release from RBCs have been associated with a systemic proinflammatory cytokine response, in particular involving tumor necrosis factor-alpha (TNF-α), interleukin-1, and interferon-gamma (IFN-γ), which in turn elevate core temperature and cause fever. A small proportion of trophozoites develop into gametocyte (sexual stage), the form that is infective to the mosquito. Both male and female gametocytes are ingested by a mosquito during a blood meal, and they combine to form zygotes in the mosquito stomach (sexual reproduction). The zygotes then invade the mosquito midgut wall and develop into oocysts which mature, rupture and release sporozoites. The sporozoites migrate to the mosquito salivary glands and are injected into the next human host during a blood meal, thus continuing the cycle.

Falciparum malaria impacts viral host dynamics in HIV-1 infected persons causing a reversible induction of replication in CD14+ macrophages. It stimulates HIV replication by increasing tumor necrotis factor (TNF) and Interleukin-6 production by activated lymphocytes. In pregnancy, coinfection Malaria-HIV is associated with a decreased Interferon-gamma production by maternal placental blood mononuclear cells causing an impairment of IL-12 production that is critical for regulation of malaria antigen-specific responses. These factors lead to an increase in HIV-1 viral load following malaria which consequently impacts disease progression and transmission risk. In women with malaria, anemia was

associated with opsonic activity. This impaired opsonic activity may contribute to anemia and a decreased immunity in pregnancy induced malaria, associated with HIV-1 infection leading to poor outcomes affecting even the infant.

Many studies suggest that HIV infected persons are at an increased risk for clinical malaria especially when immune suppression is advanced. It is certain that pregnancy is a state of high susceptibility to malaria and HIV infection increases this susceptibility. During pregnancy, the Malaria HIV-1 infection is associated with higher HIV-1 viral densities, higher parasitemia and more severe manifestations. Even after adjustments for HIV-1 viral loads, placental malaria increases the risk of mother to child transmission. All efforts to reduce malaria in the pregnant women (Intermittent Preventive Prophylaxis, Cotrimoxazole and insecticide impregnated nets) will decrease risk of adverse birth outcomes and HIV transmission.

Clinical Manifestations

Fever is the cardinal symptom of malaria. It can be intermittent with or without periodicity, or continuous. Many cases have chills and rigors. The fever is often accompanied by headache, myalgia, arthralgia, anorexia, nausea and vomiting. The symptoms of malaria can be nonspecific and may mimic other diseases like viral infections or enteric fever. Malaria should be suspected in patients residing in endemic areas and presenting with the above symptoms. It should also be suspected in those patients who have recently visited an endemic area. Children with malaria often have special clinical features that differ from those of adults. In children >2 months of age who are nonimmune, symptoms of malaria vary widely from low-grade fever and headache to a temperature of >104°F with headache, drowsiness, anorexia, nausea, vomiting, diarrhea, pallor, cyanosis, splenomegaly, hepatomegaly, anemia, thrombocytopenia, a normal or low leukocyte count, or any combination of these manifestations. Severe, high-risk malaria is characterized by a depressed level of consciousness, seizures, irregular respirations or airway obstruction, hypoxia, hypotension, tachycardia, dehydration, hypoglycemia, metabolic acidosis, and hyperkalemia.

Recrudescence after a primary attack may occur from the survival of erythrocyte forms in the bloodstream. Long-term relapse is caused by release of merozoites from an exoerythrocytic source in the liver, which occurs with *P. vivax* and *P. ovale*, or persistence within the erythrocyte, which occurs with *P. malariae*. *P. falciparum* is most commonly associated with serious complications, although milder or asymptomatic infections occur in persons with partial immunity.

Studies now show that HIV infected persons have more frequent episodes of symptomatic malaria and it in turn increases HIV viral loads and decreases CD4+ cell counts associated with dysregulation of cytokines and antibodies. There are at least ten clinical or laboratory syndromes that overlap when there is malaria HIV co-infection. Malaria and HIV-1 infections could cause neurodevelopmental impairments in children which are worsened by coexisting anemia, malnutrition and micro-nutrient deficiencies. Neonates with sepsis in areas with potential placental malaria could have congenital malaria; hence malaria blood smears for pregnant women from endemic areas become clinically important for prompt detection and treatment.

Diagnosis

Any child who presents with fever or unexplained systemic illness who has traveled or resided in a malaria-endemic area within the previous year should be assumed to have life-threatening malaria until proven otherwise. Malaria should be considered regardless of the use of chemoprophylaxis. Important criteria that suggest *P. falciparum* malaria include symptoms occurring <1 month after return from an endemic area, intense parasitemia (>2%), ring forms with double chromatin dots, and erythrocytes infected with more than one parasite.

A diagnosis of malaria is based on clinical criteria (clinical suspicion) and detection of parasites in blood (parasitological or confirmatory diagnosis).

Clinical suspicion alone has little specificity, as the signs and symptoms of malaria are nonspecific. Malaria is suspected clinically mainly on the basis of fever or a history of fever.

The following WHO recommendations are considered valid for clinical diagnosis:

- *In settings where the malaria is low*, clinical diagnosis of uncomplicated malaria should be based on the degree of exposure to malaria and a history of fever or fever in the previous three days with no features of other severe diseases.
- *In settings where the malaria is high*, clinical diagnosis should be based on fever or a history of fever in the previous 24 hours and/or the presence of anemia, for which pallor of the palms appears to be the most reliable sign in young children.

In all settings, clinical suspicion of malaria should be confirmed with a parasitological diagnosis. However, in settings where parasitological diagnosis is not possible the decision to provide antimalarial treatment must be based on the prior probability of the illness being malaria.

The two methods commonly used for parasitological diagnosis are light microscopy and rapid diagnostic tests for detecting parasite antigens. Light microscopy has the advantage of low cost in situations of high case-load and

high sensitivity and specificity when used by well-trained staff. Rapid diagnostic tests are generally more expensive, but the prices of some have decreased recently so that use is cost-effective in some settings. An operational constraint, however, is that their sensitivity and specificity are vulnerable to high temperatures and humidity. The results of parasitological diagnosis should be available within less than two hours of presentation of the patient. If this is not possible, the patient must be treated on the basis of a clinical diagnosis. In all cases, if there is a strong clinical suspicion, the case should be treated as malaria.

The WHO recommends parasitological confirmation (microscopy or rapid diagnostic test) before treatment for all suspected malaria cases. Antimalarial treatment on the basis of clinical suspicion should only be given in situations where parasitological diagnosis is not available, especially in vulnerable populations (children under five years of age and severe malaria). The choice of using rapid diagnostic tests or microscopy depends on local circumstances, including the skills available, the use of microscopy for other diseases present in the area and the case-load. Light microscopy remains the gold standard for diagnosis, and rapid diagnostic tests should be used where microscopy is not available. Both thick and thin blood smears should be examined. The concentration of erythrocytes on a thick smear is 20 to 40 times that on a thin smear and is used to quickly scan large numbers of erythrocytes. The thin smear allows for positive identification of the malaria species and determination of the percentage of infected erythrocytes. The latter is useful in following the response to therapy.

When the case-load of patients with fever is high, microscopy is likely to be less expensive than rapid diagnostic tests. Microscopy can be used to identify species, quantify parasites and identify other causes of fever. In situations where most malaria patients are treated outside the health services and in remote areas where good quality microscopy cannot be supported, rapid diagnostic tests might be useful.

The differential diagnosis includes enteric fever, rickettsial fever, viral hepatitis, encephalitis, meningitis, sepsis, leptospirosis, tuberculosis, brucellosis, yellow fever, and babesiosis.

Treatment of Uncomplicated Malaria

Treatment of P. vivax Cases

Positive *P. vivax* cases should be treated with chloroquine in full therapeutic dose of 25 mg/kg divided over three days. Vivax malaria relapses are due to the presence of hypnozoites in the liver. The relapse rate in vivax malaria in India is around 30 percent. For its prevention, primaquine should be given at a dose of 0.25 mg/kg daily for 14 days under supervision. Primaquine is contraindicated in G6PD deficient patients, infants and pregnant women, as it causes hemolysis in this population. Caution should be exercised before administering primaquine in areas known to have high prevalence of G6PD deficiency; therefore, it should be tested if facilities are available. The patient should be advised to stop primaquine immediately if he/she develops symptoms like dark-colored urine, yellow conjunctiva, bluish discoloration of lips, abdominal pain, nausea, and vomiting.

Treatment of P. falciparum Cases

The treatment of *P. falciparum* malaria is based on areas identified as chloroquine resistant or cholorquine sensitive. Artemisinin Combination Therapy (ACT) should be given in resistant areas whereas chloroquine can be used in sensitive areas. ACT should be given only to confirmed *P. falciparum* cases found positive by microscopy or rapid diagnostic tests.

ACT consists of an artemisinin derivative combined with a long acting antimalarial (amodiaquine, lumefantrine, mefloquine or sulfadoxine-pyrimethamine). The ACT used in the national program in India is artesunate and sulfadoxine-pyrimethamine (SP). Presently, artemether and lumefantrine fixed dose combinations and blister packs of artesunate and mefloquine are also available in India. Artemisinin derivatives must never be administered as monotherapy for uncomplicated malaria. These rapidly acting drugs, if used alone, can lead to development of parasite resistance.

Severe Malaria

Clinical Features

Severe manifestations can develop in *P. falciparum* infection over a span of time as short as 12 to 24 hours and may lead to death, if not treated promptly and adequately.

Severe malaria is characterized by one or more of the following features:

- Impaired consciousness/coma
- Repeated generalized convulsions
- Renal failure (serum creatinine >3 mg/dl)
- Jaundice (serum bilirubin >3 mg/dl)
- Severe anemia (Hb <5 g/dl)
- Pulmonary edema/acute respiratory distress syndrome
- Hypoglycemia (plasma glucose <40 mg/dl)
- Metabolic acidosis
- Circulatory collapse/shock (Systolic BP <80 mm Hg, <70 mm Hg in children)

- Abnormal bleeding and DIC
- Hemoglobinuria
- Hyperthermia (Temperature >104°F)
- Hyperparasitemia (>5% parasitized RBCs in low endemic and >10% in hyperendemic areas).

Parenteral artemisinin derivatives or quinine should be used irrespective of chloroquine sensitivity.

- **Artesunate:** 2.4 mg/kg IV or IM given on admission (time = 0), then at 12 and 24 hours, then once a day. Care should be taken to dilute artesunate powder in 5 percent sodium bicarbonate provided in the pack.
- **Quinine:** 20 mg quinine salt/kg on admission (IV infusion in 5 percent dextrose/dextrose saline over a period of 4 hours) followed by maintenance dose of 10 mg/kg 8 hourly; infusion rate should not exceed 5 mg/kg per hour. Loading dose of 20 mg/kg should not be given, if the patient has already received quinine. A bolus injecton of quinine should never be given. If parenteral quinine therapy needs to be continued beyond 48 hours, dose should be reduced to 7 mg/kg 8 hourly
- **Artemether:** 3.2 mg/kg IM given on admission then 1.6 mg/kg per day.
- **α β Arteether:** 150 mg daily IM for 3 days in adults only (not recommended for children).

Once the patient can take oral therapy, the further follow-up treatment should be as follows: Patients receiving parenteral quinine should be treated with oral quinine 10 mg/kg three times a day to complete a course of 7 days, along with doxycycline 3 mg/kg per day for 7 days. (Doxycycline is contraindicated in pregnant women and children younger than 8 years of age; instead, clindamycin 10 mg/kg 12 hourly for 7 days should be used).

Patients receiving artemisinin derivatives should receive a full course of oral ACT.

However, ACT containing mefloquine should be avoided in cerebral malaria due to neuropsychiatric complications.

For management of severe malaria, supportive treatment includes parenteral antibiotics, anticonvulsants, antipyretics, intravenous fluids, blood transfusion and oxygen.

Response to antimalarial treatment is more effective if the person has had some past immunity to malaria. Among medications used for malaria and HIV-1 infections, at least 12 medications have potential drug interactions and overlapping toxicities. Relatively new studies have demonstrated that artemisinin, sulfadoxine-pyrimethamine (SP), and artemether-lumefantrine are less effective in HIV infected versus uninfected persons though there are issues that this reflects rapid new infections rather than relapses of old infections or failure of treatment. Reduced concentrations of artemether and lumefantrine occur while coadministered with the NNRTI drugs nevirapine and efavirenz. This increases the risk of failure of treatment. While on PIs or the uncommonly used NNRTIs, delavirdine, halofantrine, artemether, and lumefantrine are contraindicated mainly for toxicities. Quinine has been on the list of potential drug interactions but not much has been documented.

It is observed that HIV is more prevalent in populations that have severe anemia due to malaria. With the risk of bacteremia being common in this population, there should be a low threshold for antibiotics when the child is HIV infected and with severe anemia due to malaria.

Complications

Cerebral malaria is a serious complication of *P. falciparum* infection that is most common among children and nonimmune adults. It usually develops after the patient has been ill for several days and may develop precipitously. Cerebral malaria is associated with a fatality rate of 20 to 40 percent but rarely causes long-term sequelae if treated appropriately. As with other complications, cerebral malaria is more likely among patients with parasitemia of >5 percent. The symptoms always include a decreased level of consciousness and range in severity from drowsiness and severe headache to confusion, delirium, hallucinations, or deep coma. Physical findings may be normal or may include fever to 106-108°F, seizures, muscular twitching, rhythmic movement of the head or extremities, contracted or unequal pupils, retinal hemorrhages, hemiplegia, absent or exaggerated deep tendon reflexes, and a positive Babinski sign. Lumbar puncture reveals increased pressure and cerebrospinal fluid protein with minimal or no pleocytosis and a normal glucose concentration. There are no specific electroencephalographic findings with cerebral malaria.

Renal failure is a common complication of severe *P. falciparum* malaria and results from deposition of hemoglobin in renal tubules, decreased renal blood flow, and acute tubular necrosis. **Blackwater fever** is a clinical syndrome that consists of severe hemolysis, hemoglobinuria, and renal failure. It is a rare complication that occurs when the combination of antibody directed against parasite-laden erythrocytes and complement result in severe hemolytic anemia, hemoglobinuria, oliguria, and jaundice. Renal failure usually requires peritoneal dialysis or hemodialysis. Pulmonary edema may occur several days after therapy has begun and is commonly associated with excessive intravenous therapy. It can develop rapidly and may be fatal. Thus, great care should be taken not to overhydrate patients with *P. falciparum* malaria.

Hypoglycemia is a complication of malaria that is more common in children, pregnant women, and patients receiving quinine therapy. Patients may have a decreased level of consciousness that can be confused with cerebral malaria. Hypoglycemia is associated with increased mortality and neurologic sequelae.

Thrombocytopenia is a common complication of *P. falciparum* and *P. vivax* malaria. Although significant bleeding is uncommon without DIC, platelet counts can decrease to 10,000–20,000/mm^3. **Splenic rupture** is a rare complication that may occur with acute infection owing to any malaria species. Splenic rupture can occur spontaneously but is usually the result of trauma that includes overly vigorous palpation on physical examination. It causes severe internal hemorrhage and may result in death if removal of the spleen and blood transfusion are not performed in a timely manner. **Algid malaria** is a rare form of *P. falciparum* malaria that occurs with overwhelming infection, hypotension, hypothermia, rapid weak pulse, shallow breathing, pallor, and vascular collapse. Death may occur within a few hours.

Among children living in endemic areas, malarial attacks adversely affect the educational attainment of the school going child. Prevention of attacks significantly improves educational attainment.

Prevention

Malaria prevention consists of reducing exposure to infected mosquitoes and chemoprophylaxis.

For short-term chemoprophylaxis (less than 6 weeks)

Doxycycline: 100 mg daily in adults and 1.5 mg/kg for children more than 8 years old. The drug should be started 2 days before travel and continued for 4 weeks after leaving the malarious area.

Note: Doxycycline is contraindicated in pregnant women and children less than 8 years.

For long-term chemoprophylaxis (more than 6 weeks)

Mefloquine: 5 mg/kg body weight (up to 250 mg) weekly and should be administered two weeks before, during and four weeks after leaving the area.

Note: Mefloquine is contraindicated in cases with history of convulsions, neuropsychiatric problems and cardiac conditions.

Protease Inhibitor Antiretroviral drugs (saquinavir, ritonavir, indinavir) directly inhibit the growth of *Plasmodium falciparum in vitro*. These drugs hence have clinical significance as having potential prophylaxic activity against both *P. vivax* and *P. falciparum*.

Cotrimoxazole is a commonly utilized prophylactic drug used in HIV infected persons. It has a similar action to sulfadoxine-pyrimethamine used in malaria which in turn has clinical implications. Pregnant HIV infected women in malaria endemic areas need intermittent prophylaxis but ideally not with sulfadoxine-pyrimethamine if they have been on cotrimoxazole prophylaxis previously due to the possibility of cross-resistance. In addition, widespread use of cotrimoxazole is a theoretical risk factor for the development of cross resistance to sulfadoxine pyrimethamine in the future.

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2.18

Immune Reconstitution Inflammatory Syndrome in Children

James JC Nuttall

Introduction

Antiretroviral therapy (ART) results in the restoration of cell-mediated immunity, reduction in the frequency of opportunistic infections and significant improvement in the survival of HIV infected individuals. Although the majority of patients show rapid clinical improvement following the initiation of ART, a smaller proportion undergoes early clinical deterioration during recovery from severe immune deficiency. This phenomenon was first described in HIV infected patients treated with zidovudine monotherapy in whom a localized form *Mycobacterium avium intracellulare* infection presented 1-2 weeks after starting treatment.[1] Immune Reconstitution Inflammatory Syndrome (IRIS), also referred to as Immune Restoration Disease (IRD), describes a paradoxical clinical deterioration caused by an exaggerated inflammatory immune response to infectious or non-infectious antigens. IRIS may occur in the context of treated or untreated infections such as mycobacteria, fungi and herpes viruses, and typically presents during the period following ART initiation in the presence of a rising CD4 count and a decreasing HIV viral load.[2] IRIS is not specific to ART and similar reactions may occur in leprosy and tuberculosis in HIV uninfected individuals following the initiation of antimycobacterial therapy.[3]

The pathophysiology of ART-associated IRIS is not completely understood and the varied clinical manifestations reflect diverse immunopathological mechanisms. Recovery of specific immune responses to pathogens or antigens, and immune 'dysregulation' with overproduction of Th1 cytokines has been proposed as important mechanisms.[4,5]

IRIS encompasses diverse manifestations although infectious causes of IRIS predominate. IRIS in children has mostly been reported in association with mycobacterial organisms, varicella zoster virus, herpes simplex virus, cutaneous mycoses, progressive multifocal leucoencephalopathy, and Cryptococcus neoformans.[6-9]

A number of clinical scenarios have been recognized in ART-associated IRIS. In 'unmasking' IRIS there is an underlying subclinical or previously unrecognized infection which flares after starting ART. 'Paradoxical' IRIS presents with an exacerbation of a past known and often treated infection following ART initiation.[10] IRIS may also manifest as an autoimmune condition such as Graves' disease and Guillain-Barrè syndrome, as an inflammatory reaction at the site of a malignancy such as Kaposi sarcoma, or directed at an unknown antigen such as in sarcoidosis.

Basic Pathophysiology

IRIS appears to result from restoration of immunocompetence but this process varies between individuals and the immunological environment in the weeks and months after starting ART is influenced by many factors. Patient factors include age, nutritional state and coinfections; pathogen factors include the nature of the infecting organism (viruses, bacteria, intracellular pathogens, fungi, and parasites), site of infection and the presence of drug resistance. The nature and degree of HIV mediated immune dysfunction prior to starting ART is influenced by the duration and route of infection, and pathogenicity of the HIV strain. HIV mediated immune dysfunction after starting ART is influenced by the efficacy of the ART regimen. The genetic associations of IRIS differ according to the causative agent(s) involved.[4]

The clinical diversity of IRIS is thought to reflect diverse immunopathological mechanisms.[4] IRIS associated with intracellular pathogens, including mycobacteria, cryptococci, Histoplasma species and Leishmania species, was characterized using delayed-type hypersensitivity immune responses to skin testing with mycobacterial antigens, and granulomatous inflammation in tissue samples. Subsequent studies have identified pathological overproduction of Th1 cytokines,

particularly gamma interferon, in association with IRIS to intracellular pathogens. By contrast, CD8 T cell responses in the central nervous system have been identified in IRIS due to varicella zoster virus or the JC polyoma virus that causes progressive multifocal leukoencephalopathy. Hepatitis C virus (HCV)-associated IRIS is likely to reflect a pathogen-specific immune response as titres of antibodies to HCV core antigen rise in parallel to alanine aminotransferase (ALT) levels and plasma markers of T cell activation.[4]

The majority of HIV infection in infants and children occurs as a result of vertical transmission during the antenatal or peripartum period. Immaturity of the immune system coupled with severe HIV related immunosuppression may prevent development of effective T cell specific immune responses and immunologic memory to infecting pathogens. The capacity for immunologic memory in infants is likely to vary with different pathogens and thus influence whether IRIS is of the unmasking or paradoxical type. For example, newborns develop BCG-specific T cell responses following BCG vaccination and immunosuppressed HIV infected children restore antimycobacterial immune responses after starting ART.[11] Accumulation of clinically inapparent infective organisms may occur during the period prior to starting ART. Unlike adults, immune repopulation after ART predominantly involves naive CD4 cells rather than memory CD4 cells and this may be due to the presence of a functional thymus in young children.[12] Recovery of immune system capacity to generate pathogen-specific responses and mount an inflammatory reaction leads to one or more of the clinical manifestations recognized as IRIS. Mycobacterial and herpes virus infections are well recognized IRIS events but other causes of clinical deterioration and death following ART initiation such as presumed or proven bacterial sepsis may also occur as a result of 'unmasking' IRIS although further evidence to support this hypothesis is required.

Adolescents and adults who become infected with HIV later in life by horizontal transmission have typically had a period of relative immune maturity and competence during childhood and early adulthood and developed mature T cell specific immune responses together with immunologic memory to a wide array of pathogens. They may subsequently also accumulate significant antigenic burden during the pre-ART period of increasing immune suppression. After starting ART they are more likely to develop the 'paradoxical' form of IRIS as a result of amplification of pre-existing immunologic memory. This scenario may present clinically as symptomatic relapse despite initial improvement representing antigen-driven immune activation with few or no detectable organisms and sterile cultures due to effective treatment of the opportunistic infection.[10]

Combined clinical and laboratory studies are needed in order to better understand the pathophysiology of IRIS in infants and children. Such studies should seek to establish evidence of both immunologic memory to common IRIS pathogens prior to initiation of ART and a pathogen-specific clinical and immunologic 'signature' of IRIS whether it be 'unmasking' or 'paradoxical' in nature. The IMPAACT P1073 study on IRIS pathogenesis will hopefully address a number of these issues.[13]

Epidemiology

A systematic review and meta-analysis of 54 cohort studies from 22 countries incorporating 13,103 adult patients reported that 16.1 percent of unselected adult patients starting ART developed any type of IRIS. IRIS developed in 37.7 percent of those with cytomegalovirus retinitis, 19.5 percent of those with cryptococcal meningitis, 16.7 percent of those with progressive multifocal leukoencephalopathy, and 15.7 percent of those with tuberculosis, 12.2 percent of those with herpes zoster, and 6.4 percent of those with Kaposi sarcoma. 4.5 percent of patients with any type of IRIS died, 3.2 percent of those with tuberculosis-associated IRIS died, and 20.8 percent of those with cryptococcal meningitis died.[14] Adult IRIS cases in comparison with controls have been identified as having significantly lower CD4 counts at baseline and at the time of IRIS diagnosis, but similar virological and immunological responses to ART overall. There is a high risk of IRIS in adult patients with fewer than 50 cells per μL at ART initiation.[15]

Table 2.18.1 summarizes some of the important pediatric epidemiological studies. The incidence of all forms of IRIS in children has been reported as 11.5-21 percent, however, studies have used different IRIS case definitions.[6-9] The frequency and spectrum of manifestations varies by region and age of children at ART initiation. Cutaneous herpes virus infections predominated in two reports from the USA and Peru[6,9] where the mean age at ART initiation was 5-7 years. IRIS events associated with mycobacterial species, including *M. tuberculosis*, *M. bovis* and nontuberculous mycobacteria, have been commonly reported in children from resource-limited settings[7-9,16-22] reflecting the large burden of mycobacterial disease. *Bacillus Calmette Guerin* (BCG)-associated IRIS was the commonest IRIS event reported in a South African cohort of children less than two years of age at ART initiation.[8] BCG-associated IRIS has predominantly been reported from Thailand[7,19] and South Africa: 6-14.8 percent of children starting ART in three separate cohorts from South Africa developed BCG IRIS.[8,20,21] Other case reports have identified *C. neoformans* and Guillain Barre syndrome,[6] progressive multifocal leukoencephalopathy (PML) due to JC virus,[23] and sarcoidosis[24] associated with IRIS.

Table 2.18.1: IRIS epidemiological studies

	Tangsinmankong, 2004 USA[6]	*Puthanakit, 2006 Thailand*[7]	*Smith, 2009 South Africa*[8]	*Wang, 2009 Peru*[9]
Age of children (at start of ART)	Mean 6.9 years (± 5.17)	Mean 7.19 years (range 2-15 years)	Median 8 months (range 2-24 months)	Mean 6 years (range 4 months-16 years)
IRIS incidence (n = total pts. starting ART in cohort)	11.5% (n = 61)	19% (n = 153)	21% (n = 162)	20% (n = 91)
Time to IRIS event (after start of ART)	Mean 13 weeks (range 5-24 weeks)	Median 4 weeks (range 2-31 weeks)	Median 16 days (range 7-115 days)	Median 6.6 weeks (range 2-34 weeks)
Baseline parameter (Mean ± SD) CD4 % IRIS cases Controls CD4 count (cells/mm^3) IRIS cases Controls HIV/RNA ($\log_{10}$ copies/ml) IRIS cases Controls	9.4 (±13.6), n = 7 23.6 (±12.8), n = 54 p <0.05 191 (±316.9), n = 7 769 (±682.7), n = 54 p <0.05 4.68 (±0.3), n = 7 4.35 (±0.1), n = 54 p >0.05	3.1 (±3.9), n = 29 5.5 (±4.8), n = 124 p = 0.02 5.37 (±0.4), n = 25 55.37 (±0.4), n = 103 p > 0.05	Median 13.95 (IQR 9.2-22.1), n = 34 Median 19.2 (IQR 13.5-24.8), n = 128 p = 0.009 741 (±753), n = 34 1075 (± 688), n = 128 p = 0.015 >5.88: 26 (79%), n = 33 <5.88: 66 (55%), n = 120 p = 0.04	8.9 (±5.6), n = 18 5.3 (±9.5), n = 73 p = 0.15 288 (±395), n = 7 239 (±247), n = 73 p = 0.50 5.17 (±0.64), n = 18 5.52 (±0.56), n = 73 p = 0.02
No. of children with IRIS	7	29	34	18
Total no. of IRIS events (some children had >1 IRIS event)	7	32	41	18
IRIS events (% age of total IRIS events)	Varicella zoster (100%)	Mycobacteria (44%) Varicella zoster (22%) Herpes simplex (22%) Cryptococcal meningitis (9%) Guillain Barre syndrome (3%)	Mycobacteria (88%) BCG (67%) TB (33%) BCG and TB (17%) *S. pneumonia* infection (5%) Cytomegalovirus pneumonitis (2%) Herpes simplex (2%) Severe seborrheic dermatitis (2%)	Varicella zoster (33%) Herpes simplex (33%) *M. tuberculosis* (28%) BCG adenitis (6%)
Deaths IRIS cases Controls	0 1 (2%)	3 (10%) 2 (2%)	3 (9%) 14 (11%)	0 0

Studies have identified various risk factors relevant to the development of IRIS in different clinical settings. Amongst infants less than 2 years of age, younger age at the time of starting ART was identified as an important risk factor for BCG-IRIS[8,20] but age at ART initiation has not been an important factor amongst older children with other IRIS conditions. Lower baseline CD4 percentage and CD4 absolute count was a risk factor for IRIS in some but not other studies.[6-9,20,21] Moderate to severe malnutrition at the time of ART initiation has been reported as a significant independent risk factor for the development of IRIS in children.[8,9] In one study IRIS cases had lower sex-adjusted and age-adjusted weight-for-age Z-scores at baseline than non-IRIS controls with 82 percent of IRIS cases being below –2 SD below the mean compared with 49 percent of controls ($p = 0.0005$).[8] Gender, HIV clinical stage (assessed by CDC or WHO classification systems) and ART regimen have not been shown to predict the development of IRIS.[6-9]

There is limited and conflicting data on immunological and virological response to ART and its association with IRIS in children. One study reported that children who developed herpes zoster IRIS showed a significantly greater increase in CD4 + T cell percentage and a greater reduction in HIV RNA levels at 3 months after initiation of ART than those without IRIS.[6] Another study showed no significant difference in CD4 percentage or HIV RNA levels between IRIS and non-IRIS cases at 8, 12 and 24 weeks after initiation of ART in 77 Thai children.[7] A South African study reported significantly higher HIV RNA values after 6 months of ART in children who developed IRIS compared to controls (62%) of IRIS cases had viral load > 400 copies/ml at 6 months compared with 28 percent of controls ($p = 0.001$). The authors speculated that drug-drug interactions and compromised adherence related to the addition of anti-tuberculous drugs may account for the finding.[8] Although deaths have occurred in association with IRIS events in a number of studies, significant excess mortality due to IRIS has not been reported.

IRIS in Resource-limited Settings

Although the availability of ART has increased significantly in developing countries since 2004, many infants and children still fail to access treatment and for those who do, advanced clinical disease and/or advanced immunosuppression at the time of starting ART is common. Screening for opportunistic infections, and prophylaxis or treatment of these infections, particularly mycobacterial infections, may be suboptimal. Large numbers of children are thus at high risk for developing IRIS. Refeeding syndrome during the recovery phase of malnutrition has also been reported as a contributory factor to IRIS.[42]

Although IRIS has not clearly been associated with increased mortality rates in children, lack of awareness of the syndrome may have led to under-recognition and under-reporting. The consensus case definition of IRIS in children that was recently proposed is likely to increase awareness and facilitate further studies.[10] Evidence-based management and prevention strategies that are applicable in resource-limited setting where the majority of IRIS events occur are urgently required.

IRIS Case Definition

Since the first reports of ART-associated IRIS began appearing in the literature, epidemiological studies have made use of various different definitions of IRIS. Atypical clinical manifestations of opportunistic infections not seen in ART-naive patients and new AIDS-defining events or deaths after initiation of ART with or without evidence of variable virological and immunological responses to ART were reported.

There are currently no confirmatory tests for the diagnosis of IRIS. The International Network for the Study of HIV associated IRIS (INSHI) has developed working consensus case definitions of general IRIS, TB-IRIS, and pediatric TB-IRIS which have been published and are available on the website.[10,25,26] Case definitions for cryptococcal IRIS are in development.

The general IRIS case definition incorporates three major consensus criteria:
- Response to ART
  - Receiving ART
  - Virological response > 1 $\log_{10}$ copies/ml decrease in HIV RNA (if available).
- Clinical deterioration of an infectious or inflammatory condition temporally related to ART initiation.
- Symptoms that cannot be explained by:
  - The expected clinical course of a previously recognized and successfully treated infection
  - Medication side-effect or toxicity
  - Treatment failure
  - Complete nonadherence.

Although virological response to ART is included as a diagnostic criterion, HIV RNA monitoring is frequently not available in resource-limited settings and this should not deter clinicians from making a well-informed, strongly suspected clinical diagnosis in the right setting.

Tables 2.18.2 and 2.18.3 provide details of the criteria for the diagnosis of pediatric TB-IRIS.[26]

Table 2.18.2: Consensus case definition for diagnosis of pediatric TB-IRIS [26]

Criterion	*Definition of criterion*
Evidence of clinical response to ART	Virologic response with >1 $\log_{10}$ copies/ml decrease in HIV RNA (if possible)[a]
Clinical deterioration from an infectious or inflammatory condition temporally related to the initiation of ART	Unmasking IRIS requires a new active diagnosis[b]. For paradoxical TB-IRIS, refer to Table 2.18.3 for clinical criteria
Symptoms cannot be explained by:	An alternate infection or neoplasm/treatment failure of the opportunistic infection[c]/adverse drug reaction/complete noncompliance to ART or TB treatment[d]

[a] IRIS can occur in the absence of a meaningful rise in CD4 count. In ART naive persons, an initial virologic response generally always occurs. In non-naive persons or with known ART resistance, proof of virologic response becomes more important.

[b] Unmasking caveats: Active infections, such as TB, should be excluded at time of ART initiation. Diagnosis of incident TB infections should conform to national or WHO guidelines. In children, bacteriologic confirmation may not always be achieved. Unmasked incident infections may have accelerated presentations with exaggerated symptoms. Refeeding syndrome of malnourished children may contribute to unmasking opportunistic infections. Generally occurs within 6 months after ART initiation.

[c] Paradoxical IRIS can occur with multi-drug-resistant and extensive drug-resistant TB; however, the primary concern is the efficacy of the TB therapy. For TB-IRIS, noncompliance and TB treatment failure are critical to exclude.

[d] Even with imperfect ART compliance and lack of HIV virologic suppression, immunologic reconstitution and CD4 rise can occur temporarily.

Table 2.18.3: Infectious or inflammatory clinical criteria for paradoxical TB-IRIS[26]

	Criteria: at least one major clinical criterion or two minor clinical criteria are required
Major criteria	New or enlarging lymph nodes, fistulas, cold abscesses, or other focal tissue involvement New or worsening radiological features of TB New or worsening central nervous system TB (meningitis, or focal neurological deficit) New or worsening TB serositis (pleural effusion, ascites, or pericardial effusion) or arthritis Signs of tuberculin hypersensitivity (e.g. phlyctenular conjunctivitis, erythema nodosum)
Minor criteria	New or worsening constitutional symptoms such as fever, night sweats, or weight loss New or worsening respiratory symptoms such as cough, dyspnea, or stridor New or worsening abdominal pain, discomfort, or distension with or without palpable mass including hepatosplenomegaly Resolution of clinical or radiological findings of the suspected IRIS episode without change in ART, TB treatment, or additional antimicrobial therapy
Supportive observations	Conversion of TST negative to positive in patients receiving TB treatment and ART at time of an IRIS event, or >5 times increase from baseline in interferon release assay (e.g. QuantiFERON, ELISPOT), Opinion

ELISPOT: Enzyme-linked immunosorbent spot, TST: Tuberculin skin test

Clinical Presentation and Diagnosis of Common IRIS Conditions

Bacillus Calmette Guèrin (BCG)-associated IRIS

BCG vaccine-associated disease occurs in HIV infected and uninfected children, and has been increasingly described in association with IRIS. A classification system of BCG vaccine-associated disease was proposed by Talbot[28] and modified by Hesseling et al[29] as follows:

- ***Local disease:*** BCG injection site abscess or scar ulceration.
- ***Regional disease:*** Ipsilateral regional lymph node involvement that may include enlargement, suppuration and fistula formation.
- ***Distant disease:*** Involvement of any site beyond local or regional ipsilateral process with BCG confirmation, e.g. pulmonary secretions, cerebrospinal fluid, osteitis or distant skin lesions.
- ***Disseminated BCG disease:*** BCG confirmed from >1 distant site and/or from at least 1 blood or bone marrow culture.

Based on prospective hospital and population-based surveillance studies between 2004 and 2006 in South Africa, the estimated risk of disseminated BCG (dBCG) disease in HIV infected infants is 992 per 100 000 (95% confidence interval 567-1495) several hundred fold higher than the documented risk in HIV uninfected infants.[30,31]

BCG-IRIS is described as BCG disease that presents in an HIV infected child within three months after the initiation of ART with or without proof of immune reconstitution.[28] As indicated in Table 2.18.4, reports of BCG-IRIS from the pediatric literature predominantly describe local and regional BCG disease typically presenting 2-6 weeks after starting ART with very few cases of distant/disseminated disease. BCG-IRIS is mainly a disease of infants (<12 months of age) but does also occur in older children.

The diagnosis of local or regional BCG-associated disease, including BCG-IRIS, is frequently made on clinical grounds only. Aspiration of vaccine injection site abscesses or ipsilateral axillary or regional lymphadenitis

Table 2.18.4. Comparative data from selected studies reporting IRIS in association with BCG in children

	Puthanakit, 2005 Thailand[19]	*Nuttall, 2008 South Africa*[20]	*Smith 2009 South Africa*[8]
Age of children (median months)	96 (range 10-108)	5 (IQR 3.8-8.5)	6 (IQR 4-9)
No of BCG-IRIS events	4	21	24
Prevalence of BCG-IRIS	3% (4/150)	6% (21/352)	14.8% (24/162)
Baseline CD4 percentage (median)	2 (range 0-13)	12.3 (IQR 8.8-16.3)	-
Time to IRIS event (median)	6 week (range 4-10)	34 days (IQR 15-60)	14 days (IQR 12-27)
Local/regional disease	4 (100%)	21 (100%)	23 (96%)
Suspected distant/disseminated disease	0	1	1
Diagnosis			
M. bovis BCG confirmed by culture/PCR of:			
• Pus/nodal aspirate from local/regional adenitis/abscess	2 (50%)	7 (33%)	0*
• Blood/bone marrow/gastric aspirate/other tissue	-	1 (5%)	0*
• Clinical only	2 (50%)	14 (66%)	12 (50%)
Management			
• Observation only	1 (25%)	8 (38%)	6 (25%)
• Diagnostic or therapeutic aspiration/ drainage of abscess	3 (75%)	9 (43%)	11 (46%)
• Antimycobacterial drugs	3 (75%)	10 (48%)	17 (70.8%)
Deaths	0	0	3 (uncertain whether attributable to BCG disease)

**In this study, ten subjects were positive for acid fast bacilli and/or positive culture for M.tuberculosis complex. M. tuberculosis complex can only be differentiated into M. tuberculosis or BCG by PCR or biochemical techniques*

or abscesses for diagnostic confirmation and therapeutic reasons is also commonly practiced. Aspirated pus or nodal material should be sent for gram stain and bacterial culture as well as for TB stain and culture. The diagnosis of distant/disseminated BCG disease requires laboratory confirmation.

Routine identification of mycobacterial isolates in clinical laboratories involves culture of *Mycobacterium tuberculosis* complex, which consists of a number of species, including *M. tuberculosis, M. bovis,* and the vaccine strain, *M. bovis* BCG. Misdiagnosis of BCG disease may occur in settings of high TB and HIV prevalence, where BCG vaccination is routinely administered, and where laboratory differentiation of *M. bovis* BCG strain from *M. tuberculosis* is not available or routinely performed.[28] BCG-IRIS and TB-IRIS may occur in the same patient at the same time.[8,21]

Mycobacterium Tuberculosis-associated IRIS

Data on TB-IRIS in children is limited to a few cohort studies and case reports or small case series.

Rates of exposure to TB may be very high amongst HIV exposed infants and children, and TB disease rates of 1596 cases per 1,00,000 HIV infected infants have been documented in South Africa.[31] Post-ART TB rates of 3.4-6.2 percent have been reported in African children.[18]

Post-ART TB includes patients with incident TB disease and patients with unmasking TB-IRIS but they may be difficult to differentiate. Both require a new diagnosis of active TB disease; unmasking IRIS also requires evidence of a clinical response (ideally virological response with >1 $\log_{10}$ reduction in HIV RNA) to ART.[10] Virological monitoring is unavailable in many resource-limited settings and clinical parameters such as weight gain may be useful in differentiating TB-IRIS from incident TB but requires further study. Exposure to TB shortly after initiation of ART and subsequent clinical presentation with post-ART TB-IRIS has also been described.[32]

As indicated in Table 2.18.5, unmasking IRIS has been more commonly reported than paradoxical IRIS in children and usually presents 3-6 weeks after starting ART. The frequency of unmasking IRIS relates to the overall prevalence of TB in a specific region and the capacity of an ART program to screen for and diagnose TB in HIV infected children, both prior to initiation of ART and during follow-up on ART.

The diagnosis of pediatric TB is challenging but should conform to WHO or national TB program guidelines. Reasons for under-diagnosis of TB in HIV infected children include:

1. The non-specific nature of symptoms and signs of TB disease (persistent cough, fever, failure to thrive, abnormal chest findings).
2. Overlap with HIV disease symptoms thereby reducing the sensitivity of clinical scoring tools.
3. Poor sensitivity of tuberculin skin testing in immunosuppressed children.
4. Overlap in the radiological appearance of TB and HIV associated lung diseases including lymphocytic interstitial pneumonitis (LIP).

Table 2.18.5: Comparative data from selected studies reporting IRIS in association with mycobacterial disease (excluding BCG-IRIS events) in children

	Puthanakit, 2006 Thailand[7]	*Zampoli, 2007 South Africa*[16]	*Wang, 2009 Peru*[9]
Age of children (median)	7.5 years (range 3-12)	43 months (range 3-121)	12 months (range 8-132)
No. of TB-IRIS events	12	11	5
Baseline CD4 percentage (median)	1.5 (range 0-4)	10.3 (range 0.7-26.8)	-
Time to IRIS event (median)	4 week (range 2-21)	24 days (range 6-105)	42 days (range 14-196)
Pulmonary disease	5/12	9/11	2/5
Lymphadenitis/subcutaneous abscess/ extrapulmonary disease	7/12	2/11	3/5
Both	-	1/11	2/5
Mycobacterial diagnosis			
Definite (culture-confirmed or PCR +)	10/12	4/11	4/5
Probable TB	2/12	7/11	1/5
Unmasking IRIS	9/12 (75%)	7/11 (64%)	4/5 (80%)
Paradoxical IRIS	3/12	4/11	1/5
Deaths	2/12	1/11	0/5

5. Limited capacity to collect appropriate biological samples (induced sputum, gastric lavage, lymph node aspirates) for microbiologic testing.
6. Relatively low yield of TB smear and culture tests. Culture-positive yields of up to 40 percent reported from research settings may not be achievable in routine clinical practice.[33,34]

Negative results on tuberculin skin testing, interferon-gamma release assays and microbiologic investigations do not exclude TB and investigations are relatively expensive.

From a clinical perspective, unmasked TB infections may have an accelerated presentation with exaggerated symptoms and signs associated with significant inflammation. Pulmonary TB is the commonest form of unmasking TB and clinical manifestations reported include new or enlarging intrathoracic lymphadenopathy with or without trachea-bronchial compression, parenchymal infiltrates on chest radiography and pleural effusion. Subcutaneous lymphadenitis and TB meningitis are also reported. Tuberculin skin test conversion from negative pre-ART to positive at the time of the suspected IRIS event is considered supportive evidence of reconstitution of an anti-mycobacterial immune response but is frequently not found and is not a prerequisite for the diagnosis of unmasking TB-IRIS.[10] In the few reported cases, mycobacterial cultures were more frequently positive in unmasking as compared to paradoxical IRIS events.[16]

In paradoxical TB-IRIS, TB is diagnosed and treatment started before initiation of ART, and clinical deterioration develops after starting ART. Table 2.18.3 lists proposed clinical criteria for paradoxical TB-IRIS and reflects clinical and radiological features reported in the literature.[16,25] There are few descriptions of neurological and abdominal pradoxical TB-IRIS in the pediatric literature although pediatric cases do occur.

In addition to paradoxical TB-IRIS, it is important to consider other causes of clinical deterioration after starting ART.

1. **Pneumonia and bacterial infections** were found to be the commonest cause of observed increased rates of hospitalisation and mortality during the first 6 months of ART in Thailand and South Africa.[35,36]
2. **Treatment failure due to drug resistant TB and/or HIV:** The rate of drug-resistant TB varies between settings but has been reported in 17 percent of HIV infected children with TB in South Africa, with 6.8 percent having resistance to both rifampicin and isoniazid.[37] However, TB in children is frequently unconfirmed microbiologically and drug sensitivity testing is not widely available, making it difficult to differentiate IRIS from poor response to TB treatment. However, IRIS has been described in both adults and children with initial favourable response to standard TB treatment subsequently found to have drug-resistant TB.[38,39] HIV resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs) following perinatal nevirapine exposure is well-documented and ART failure should be considered in settings where NNRTIs are used in first-line therapy for nevirapine-exposed children.
3. **Complete noncompliance or intolerance to ART or TB treatment** is important to assess and caregivers of young children should routinely be asked to demonstrate the correct dosing and administration of medication and describe any difficulties experienced.
4. **Adverse drug reactions mimicking TB-IRIS** are relatively uncommon in children.[35]
5. **Pharmacodynamic and pharmacokinetic factors:** Subtherapeutic plasma levels of isoniazid and rifampicin due to insufficient currently recommended dosages in children and exacerbated in HIV infected children due to malabsorption, have been reported and may contribute to poor TB outcomes and drug resistance. Rifampicin causes increased metabolism of NNRTIs and protease inhibitors leading to reduced plasma concentrations which may impact on virological outcomes. Therapeutic drug monitoring is very seldom available in resource-limited settings.

Nontuberculous Mycobacterial (NTM)-IRIS

In a Thai study, NTM were identified in seven cases of unmasking and two cases of paradoxical IRIS. Clinical features included fever, dyspnea, abdominal pain and suppurative lymphadenitis. *M. avium* complex (MAC), *M. kansasii* and *M. simae* were identified from subcutaneous or mesenteric lymphadenitis or abscesses, or pulmonary secretions. Positive cultures at the time of the IRIS event were obtained from all 7 unmasking IRIS cases but neither of the 2 paradoxical IRIS cases.[7] NTM have not been identified as a common cause of pediatric IRIS in other developing countries.

Dermatological IRIS

Herpes simplex and herpes zoster are the most commonly reported dermatological IRIS events although the pediatric literature is sparse. In one report, herpes zoster was the only IRIS manifestation identified in a cohort of 63 children.[6] All cases presented within 6 months of starting ART with clinically mild disease in the usual dermatomal distribution and responded well to oral or intravenous acyclovir therapy with no ocular, neurological or hepatic complications or persistence of chronic atypical skin lesions. Children with negative varicella-specific antibody despite a previous history of varicella, severe

immunodeficiency before starting ART, and strong immunological and virological responses to ART were found to increase the likelihood of developing herpes zoster as an IRIS event. The usual manifestation of herpes simplex-IRIS reported is herpes labialis but one case of fatal herpes simplex encephalitis has been described.[7] Other IRIS skin events include exacerbations of molluscum contagiosum, tinea capitis and viral warts.

Neurological IRIS

IRIS in association with TB of the central nervous system (CNS), cryptococcal meningitis, progressive multifocal leukoencephalopathy (PML) and herpes simplex encephalitis have been reported in the pediatric literature. Clinical features include focal neurological signs such as hemiparesis and ataxia, raised intracranial pressure and seizures. CNS imaging with contrast-enhanced CT or MRI scans to highlight areas of inflammation, together with microbiological studies on cerebrospinal fluid including PCR assays are important diagnostic components.

Management Approaches to IRIS

The diagnosis of IRIS and exclusion of other causes of clinical deterioration in an immunosuppressed child recently initiated on ART may be difficult. Viral, bacterial, mycobacterial, fungal and parasitic infections need to be considered. Recently published IRIS case definitions and diagnostic criteria are useful although these are largely untested and apply mainly to TB. Empiric antimicrobial treatment is recommended and should be guided by clinical experience and opinion as well as available laboratory investigations. Resistance of TB and other opportunistic infections to empiric treatment should be considered and investigated whenever possible.

In most instances, treatment of the identified opportunistic infection in the setting of unmasking IRIS does not differ from the usual treatment of that infection. Given that some treatment are toxic, expensive or unavailable, there may be a place for reduced duration of treatment in the context of a patient with a rapidly recovering immune system as compared to treating a patient with advanced immunosuppression who has not yet started ART but evidence is lacking.

Mild cases of paradoxical IRIS may include persistent fever, mild fluctuations in respiratory symptoms with or without associated radiological changes, and temporary exacerbation of skin lesions. Reassurance, symptomatic therapy and close clinical and appropriate laboratory monitoring for further deterioration are frequently all that is needed.

For more severe IRIS cases, anti-inflammatory therapy may be considered. Although there are no randomized controlled trials of IRIS treatment in children, corticosteroids have proven to be of benefit in adults with moderate-to-severe TB-IRIS manifestations.[40] Risks include reactivation of herpes virus infections, Kaposi sarcoma and metabolic side effects if prolonged use is necessary. Corticosteroids should be used in the setting of life-threatening space-occupying lesions such as inflammatory lymph nodes obstructing airways or intracranial swellings such as tuberculomata.

Useful therapeutic procedures include percutaneous drainage of pus from abscesses, or cerebrospinal fluid drainage in the setting of cryptococcal meningitis IRIS with raised intracranial pressure.

Anecdotal beneficial experience with the use of non-steroidal anti-inflammatory drugs, pentoxifylline, montelukast, thalidomide, infliximab and hydroxy-chloroquine has been reported in adult patients. Temporary ART interruption may be considered in life-threatening IRIS including patients with neurological involvement leading to depressed level of consciousness.

Regarding BCG-IRIS, there are no prospective studies evaluating whether antimycobacterial therapy directed against *M. bovis* BCG or anti-inflammatory therapy alters the outcome of local or regional BCG-IRIS. In a cohort of 35 children with regional BCG-IRIS, no difference in time to resolution was observed between those who received antimycobacterial therapy and/or corticosteroid treatment and those who received no medication.[21]

Antimycobacterial therapy is indicated for distant/disseminated disease as case fatality rates >70 percent have been reported in infants.[28,29] *M.bovis* BCG is inherently resistant to pyrazinamide and therapy usually comprises rifampicin, isoniazid, ethionamide or ethambutol and a fluoroquinolone such as ofloxacin. Pharmacokinetic interactions involving rifampicin and protease inhibitors or nevirapine may result in subtherapeutic antiretroviral plasma concentrations and require modification of the ART regimen adding complexity and challenging adherence.

Surgical excision or debulking of lymph nodes or inflammatory tissue has a limited role in the context of BCG-IRIS.[25] Therapeutic aspiration of pus, repeated if necessary, appears to result in less scarring and better outcome.

Prevention of IRIS

The following strategies are important in the prevention of IRIS in children:

1. ***Improved prevention of mother to child transmission (PMTCT) program:*** By reducing the number of new childhood HIV infections, the incidence of IRIS will be reduced.
2. ***Avoidance of BCG vaccination of HIV infected infants:*** The high estimated risk of dBCG disease in HIV infected children and the lack of evidence for

protective efficacy of BCG vaccine in HIV infected children led the World Health Organization (WHO) in 2007 to publish revised recommendations to defer BCG vaccination in HIV exposed infants and to avoid BCG vaccination in infants who are confirmed to be HIV infected.[31]

In many resource-limited settings, selective deferral of BCG vaccination to infants born to HIV infected women is problematic under current programmatic conditions. It may be impractical, there is a risk that HIV exposed but uninfected infants miss out on the protective benefits of early BCG vaccination and early infant HIV diagnosis is/may not be readily available. For these and other reasons, universal vaccination of newborns with BCG vaccine continues in most developing countries.

In the Dominican Republic, routine prenatal HIV rapid testing of pregnant women and avoidance of BCG in HIV exposed infants while the HIV PCR test result is awaited has been successfully introduced in a regional program.[38] More widespread implementation of a selective BCG vaccination policy could reduce and potentially eliminate the problems of dBCG and BCG-IRIS in HIV infected infants.

3. ***Enhanced screening for TB and other opportunistic infections prior to initiation of ART:*** In a Ugandan study, tuberculin skin testing prior to ART initiation reduced unmasking of TB by >50 percent although high rates of anergy were documented in children with CD4 <10 percent.[38] Routine chest radiography before starting ART in order to detect pulmonary TB is another intervention that could reduce unmasking TB-IRIS.
4. ***Prophylaxis against TB with isoniazid:*** Further studies on the efficacy of pre-exposure prophylaxis against TB with isoniazid and improved implementation of postexposure isoniazid prophylaxis for all HIV infected children.
5. ***Prevention of malnutrition:*** Moderate to severe malnutrition has been identified as a risk factor for IRIS in children and refeeding syndrome may be a contributory factor.
6. ***Earlier initiation of ART in infants:*** Advanced immunosuppression is a risk factor for the development of IRIS in children. In infants with a baseline CD4 count ≥25 percent, early ART initiation (6-9 weeks of age) is associated with a significant reduction in BCG-IRIS probably by limiting the degree of CD4 depletion.[21] This beneficial effect of early ART is likely to apply to many other forms of IRIS.
7. ***Potential prophylaxis with immunomodulatory therapy at the time of starting ART in patients at high-risk for developing IRIS:*** Although corticosteroids have been used for IRIS prophylaxis and treatment, alternative anti-inflammatory agents with better tolerability and without drug-drug interactions warrant further investigation.

Case Studies

CASE 1

A 9-year-old girl with HIV infection was referred to the clinic. Symptoms of poor appetite and weight loss were reported. The CD4 count was 29 cells/mm³ (3.38%).

1. **What further investigations are indicated prior to starting ART?**
   - Investigations for TB, including a chest X-ray and sputum for microscopy and TB culture. Tuberculin skin test (Mantoux test) may be done but is likely to be negative due to the very low CD4 count, and if positive (> 5 mm diameter of induration) may reflect previous TB infection. Full blood count and alanine aminotransferase (ALT) are recommended.

Chest X-ray (Fig. 2.18.1) was assessed as normal by the attending clinician, induced sputum was smear-negative for acid fast bacilli. Baseline full blood count and alanine amino transferase were normal. She started ART three weeks later (stavudine+lamivudine+efavirenz) after receiving adherence counseling.

2. **When should this child be reassessed and why?**
   - One to two weeks after starting ART in order to discuss adherence to medication and evaluate for IRIS.

Two weeks later she complained of tiredness, cough, fever and loss of appetite for the previous week. On examination she was pale with a temperature 38.5°C and crackles were noted in the left lung.



Fig. 2.18.1: Baseline chest X-ray taken before starting ART. Initially assessed as normal but paratracheal lymphadenopathy most likely due to TB was subsequently recognized



Fig. 2.18.2: Repeat chest X-ray taken two weeks after starting ART showing massive cardiomegaly suggestive of pericardial effusion

3. **What investigations are appropriate now?**
   • Repeat chest X-ray and hemoglobin.

The hemoglobin was 7.1 g/dl (10.2 g/dl prior to starting ART) and chest-X-ray revealed massive cardiomegaly suggestive of a pericardial effusion (Fig. 2.18.2). This was confirmed with echocardiography and 360 ml of straw-colored fluid was drained from the pericardium.

4. **What is the most likely clinical diagnosis and what is the treatment?**
   • Pericardial effusion due to unmasking of TB (TB-IRIS). Four-drug anti-TB treatment (rifampicin, isoniazid, pyrazinamide and ethambutol).

The pericardial fluid was smear-positive for acid fast bacilli. HIV viral load and CD4 count was not repeated. TB treatment was started but fever persisted and repeat echocardiogram 2 weeks later showed persistent large pericardial effusion and a further 250 ml of sero-sanguinous fluid was drained. Thickened pericardium and thick pericardial fluid was noted.

5. **What additional treatment is indicated now and why?**
   • Corticosteroid treatment for anti-inflammatory and immunomodulatory effect.

Prednisone 2 mg/kg/day was started. TB culture on pericardial fluid was positive for *M. tuberculosis* sensitive to rifampicin and isoniazid. Prednisone was continued for 5 weeks and then weaned off over 2 weeks.

After 3 months on ART, the CD4 count was 81 cells/mm^3 (7.84%) and the viral load was <400 copies/ml. She continued to gain weight and was feeling generally well but after completion of steroids, she represented with clinical features of bilateral pleural effusions, abdominal distention and hepatomegaly.



Fig. 2.18.3: Repeat chest X-ray taken 15 weeks after starting ART and 4 weeks after stopping initial 7 week course of corticosteroid treatment showing large right-sided and smaller left-sided pleural effusions

6. **What is happening and what further investigations may be useful?**
   • Recurrence of TB-IRIS after weaning off prednisone, this time, involves the chest and abdomen. This is the likely diagnosis here as this patient has a suppressed HIV viral load, is adherent to ART and TB medication and the TB isolate was found to be drug sensitive. Although 4-6 weeks of corticosteroid treatment may be effective in IRIS, prolonged or repeated courses of treatment are sometimes necessary. On review of the chest X-ray taken before starting ART, it was suggestive of paratracheal lymphadenopathy likely due to TB that had been missed. Repeat chest X-ray and abdominal ultrasound looking for evidence of abdominal TB is useful.

Chest X-ray showed bilateral pleural effusions (Fig. 2.18.3) and abdominal ultrasound showed ascites and hepatomegaly but no focal intrahepatic lesions or intrabdominal lymphadenopathy. The pericardial effusion did not reaccumulate. Prednisone was restarted and the right-sided pleural effusion was drained (550 ml of straw-coloured fluid). Prednisone was continued for 2 weeks and then weaned off over 2 weeks. She continued



Fig. 2.18.4: BCG-IRIS (local and regional disease) in an infant on ART for 3 weeks

to improve clinically and completed 12 months of TB treatment. She remained virologically suppressed and the CD4 count after 8 and 11 months on ART was 223 (13.1%) and 422 (25.3%) respectively.

Case 2[42-45]

A seven-month-old HIV infected infant with a CD4 count of 13.9 percent (171×10^6 cells/mm^3) was commenced on stavudine + lamivudine + lopinavir/ritonavir. Three weeks later he presented with marked right axillary lymphadenitis and an oozing ulcer on the right upper arm (Fig. 2.18.4).

1. **What is the most likely diagnosis?**
   - BCG-IRIS involving local (BCG vaccine site) and regional (right axillary lymphadenitis) structures. Other possibilities include staphylococcal and other non-tuberculous mycobacterial infections.
2. **How would you manage this problem?**
   - Careful history, enquiring about adherence to ART and the infant's general state of well-being including weight gain since starting ART. Clinical examination looking for features of distant/disseminated BCG disease such as subcutaneous cold abscesses, bone swelling or tenderness, abdominal distension and masses, respiratory disease. X-rays may be indicated but are generally not necessary in an otherwise well child. Needle aspiration of the lymphadenitis/abscess and culture of pus for bacteria and mycobacteria may be useful for confirmation of the clinical diagnosis and as a therapeutic modality. Repeated aspiration may be necessary. Surgical incision and drainage may be considered but is unlikely to improve the outcome. For suppurative/discharging lesions, healing with scarring occurs over a period of months.

     Antimycobacterial medication is not routinely indicated for local/regional BCG-IRIS but should be used for distant/disseminated disease or recurrent or atypical regional disease. BCG is not sensitive to pyrazinamide and treatment should include isoniazid, rifampicin, ethionamide and ofloxacin.
3. **How could this have been prevented?**
   - Avoidance of BCG immunization of HIV exposed newborns until definitive HIV testing can be carried out and subsequent avoidance of BCG immunization of HIV infected infants has been recommended by the WHO. Early infant initiation of ART for HIV infected infants (from 2-3 months of age or earlier) may also reduce the incidence of BCG complications.

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2.19

The HIV Infected Child in the Emergency Department

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Introduction

In the United States, HIV infected pediatric patients present to the emergency department (ED) 1.2 to 2 times per year.[1] Fever is, with no doubt, the most common complaint among HIV infected children presenting in an acute care setting.[1] While the HIV infected pediatric patient may present to the ED with common and well-tolerated viral infections as the general pediatric population, it is also true that less frequent bacterial or opportunistic infections may develop and lead to fatal outcomes in these group of patients. Therefore, the HIV infected pediatric patient will more often undergo laboratory or radiologic testing in the ED and will also be admitted more frequently than other children. The most prevalent complaints of the HIV infected pediatric population to the ED are summarized in Table 2.19.1.

Ideally, the HIV infected pediatric patient should have a small notebook stating the following data: clinical and immunological status, previous pathologies, current and previous HAART, current and previous antibiotic prophylaxis, latest viral load and vaccine status. The current chapter attempts to give a global view of the main conditions that may take the HIV infected child to the ED and their differential diagnosis.

The Child with Unknown HIV Infection

Seldom, a child with unknown HIV infection may seek care for the first time to an ED[2] and, perhaps, the reason for consultation may be due to a serious and potentially fatal illness. It is important for physicians working in the ED to be familiar with the family and personal history, signs and symptoms in clinical examination, common secondary conditions and characteristic findings in laboratory and radiologic studies of vertically transmitted HIV infection in children (see Chapter on the Clinical and Laboratory Manifestations of HIV Infection in Children).

Table 2.19.1: Most frequent complaints of the HIV infected pediatric patients in the emergency department

Fever	*Respiratory symptoms*
Common viral infections Bacterial infections Opportunistic infections Other causes: drugs, lymphoma HIV infection	Bacterial pneumonia Lymphoid interstitial pneumonia Neumonía intersticial linfoidea, sometimes superinfected *Pneumocystis jirovecii* pneumonia Viral respiratory tract infections, Cardiomyopathy
Skin rashes	***Focal neurologic signs or altered level of consciousness***
Petechial purpura Chickenpox/herpes zoster Toxicodermias	Seizures, Toxoplasmosis Progressive multifocal leukoencephalopathy Undifferentiated CNS Lymphoma, Stroke
Abdominal pain	***Upper respiratory tract pathology***
Abdominal mass Pancreatitis Renal colic Lactic acidosis Gastrointestinal bleeding Jaundice Esophagitis (retrosternal pain)	Otitis media Sinusitis Parotid enlargement

If HIV infection is suspected, a serologic test should be performed according to each center availability. Currently, rapid and sensitive serologic tests performed in serum, urine or saliva samples are available and inform on the serostatus of a patient within one hour.[3] Under the age of 18 months, a serologic positive test may represent transplacentally transferred HIV antibodies and a virologic test will be essential to diagnose HIV infection (see Chapter on the Diagnosis of HIV Infection in Children). Nevertheless, a severely ill patient with a clinical suspicion of HIV infection should be managed as such, even in the absence of a confirmatory laboratory test.

The HIV Infected Pediatric Patient in the Emergency Department

The most prevalent complaints of the HIV infected pediatric population to the ED are summarized in Table 2.19.1.[1] Certainly, fever is the most common cause of emergency hospital admission in this group of patients. In most cases, the pathologies that take the HIV infected to the ED do not differ from those of healthy children and do not give rise to greater complexity or severity, but it is also true that HIV infection entails an increased risk of developing rare and potentially fatal diseases that the emergency physician must be able to identify and treat (Table 2.19.2). The diagnostic approach to the child with a well controlled disease is similar to that of the healthy child.

Initially, both an exhaustive medical history of the complaint, and a thorough clinical examination are required. Besides, some other medical data are essential: history of recent exposures to ill contacts, clinical (CDC categories) and immunological situations (the *nadir* and the most recent CD4 cell count, either in percentage or absolute figures according to age), the most recent plasma HIV RNA viral load, previous pathologies, specially opportunistic infections, and treatment history, current and former, including antiretroviral drugs, but also other antibiotics used to treat or prevent opportunistic infections. Even with normal CD4 cell counts at the time of consultation, a previous history of having being diagnosed with an opportunistic infection or having received primary antibiotic prophylaxis involve a greater degree of immunosuppression and an increased risk of developing one of these conditions. Finally, it is desirable to have direct contact with the patient's usual medical team.

Fever in the HIV Infected Child

HIV has a significant deleterious effect on the maturation of the immune system of the fetus and the newborn. The early affection of the thymus in perinatal HIV infection determines a profound alteration of the T cell dependent immunity that leads to a more rapid progression of the disease and to an increased susceptibility to several infections, such as *Pneumocystis jirovecii* pneumonia (PCP) or those caused by mycobacteria, fungi and viruses. On the other hand, humoral immunity is also affected as the result of a dysfunction both in T cell mediated immune response and a polyclonal stimulation of B-cells, that leads to polyclonal hypergammaglobulinemia, to a poorer response to specific antigens and, finally, to an increased susceptibility to serious bacterial infections. Finally, some patients also show a reduced phagocytic function in neutrophils.

Table 2.19.2: Life-threatening diseases that may show an acute or subacute presentation in the ED in pediatric patients with HIV infection

- ***Respiratory distress:*** Common respiratory infections (pneumonia, bronchiolitis), *Pneumocystis jirovecii* pneumonia, CMV pneumonitis, and cardiomyopathy.
- ***Severe bacterial infections:*** sepsis.
- ***Gastrointestinal bleeding:*** Gastrointestinal infections; consider CMV disease.
- ***Seizures and/or altered level of consciousness:*** Meningitis; intracranial expansive processes and stroke are uncommon; consider toxic or metabolic disorders.

Prospective studies on the management of the febrile HIV infected child are lacking, and current available information is based on case series and experts opinion. As the healthy pediatric population, HIV infected children with fever are often diagnosed with a banal infectious condition: most of the times an upper respiratory tract infection of viral etiology. Similarly, otitis media is the most prevalent focal bacterial infection in the HIV infected pediatric patient, together with other respiratory tract infections, such as pharyngitis, sinusitis or pneumonia; other common diseases are gastroenteritis, varicella or zoster, herpes virus stomatitis, and urinary tract infections. The risk of secondary bacteremia from a focal bacterial infection in these patients is higher than in the healthy child,[4,5] even with a well-controlled infection and normal CD4 cell counts; therefore, obtaining a blood culture and cultures from the site of infection before antibiotic implementation is recommended in most cases, if not all. In the HIV infected child with recurrent bacterial infections, even if receiving HAART and with preserved immunity, intravenous polyvalent gammaglobulin therapy (250-400 mg per kg of body weight) every 3 to 4 weeks is strongly recommended.

Despite available data on fever without a source in HIV infected children is scarce, most illnesses are likely to be caused by viral infection, mild and self-limited.

However, the incidence of bacteremia or other serious complicating illnesses is also probably higher among the HIV infected child.[8] Clinical and laboratory features that identify the immunocompetent child at increased risk for occult bacteremia have not been validated in the HIV infected pediatric patient.

Immunocompromised patients are at high risk for severe bacterial infections (bacteremia, usually from a respiratory cause, sepsis, meningitis, pneumonia, osteomyelitis, visceral abscesses)[4] and opportunistic infections. In the absence of HAART, one in every 4 perinatally-HIV infected infants will develop a severe bacterial infection by the age of 6 months, and a third of them before one year of age. [8] Severe bacterial infections are usually caused by encapsulated bacteria (especially *pneumococci*, *Haemophilus influenzae* and *meningococci*), *staphylococci*, *Salmonella*, *enterococci* and *Pseudomonas*, and are more frequent during the first two years of life. Opportunistic infections,[9] with the exception in PCP, are characteristic of severe immunocompromised patients and occur later on in the evolution of the disease. The rate of serious bacterial infections in HIV infected children in the era of HAART is unknown.

The diagnostic and therapeutic approach to the pediatric patient with HIV infection and fever in the ED is summarized in algorithm1. It should be emphasized that this approach has to be individualized for each patient and should take into account both the clinical features of the patient and the ability of the family or caregivers to provide the patient with the proper treatment and follow-up.

Drug hypersensitivity syndrome is usually accompanied with rash (nevirapine and sulfonamides), hypoplastic anemia (sulfonamides) or cough and abdominal pain (abacavir). When this syndrome is suspected, the drug should be immediately discontinued (especially abacavir) and fever will normally subside within 24 to 48 hours. Although lymphoma can lead to fever, it should always represent a diagnosis of exclusion in the HIV infected pediatric patient and should be suspected in the severely immunocompromised child, with elevated lactate dehydrogenase levels and, sometimes, other clinical manifestations related to the location of the lymphoma: abdominal mass, constipation, lymphadenopathy, focal neurologic signs or symptoms, or altered level of consciousness. Patients with advanced disease may also show fever as part of the wasting syndrome, which also includes involuntary loss of body weight, diarrhea and weakness. In the pediatric patient, the wasting syndrome is also a diagnosis of exclusion, its main differential diagnosis being infections with *atypical mycobacteria* or *Cytomegalovirus*.

Gastrointestinal Problems in the HIV Infected Child

Infectious diarrhea (Table 2.19.3) is undoubtedly the most common cause of abdominal pain in pediatric patients with HIV infection. Infections of the gut usually manifest as enteritis through the production of enterotoxins (affecting the small intestine), or through direct injury to the colonic mucosa or ileocolitis (impairment of the colon). Patients with enteritis present with watery stools and frequent vomiting, the most common pathogens being *rotavirus*, *adenovirus*, enterotoxigenic *Escherichia coli* and *Giardia lamblia*. Ileocolitis is caused by enteroinvasive bacteria and usually presents with fever, colicky abdominal pain and profuse diarrhea with blood and mucus in the stools; germs commonly involved with ileocolitis are *Salmonella*, *Campylobacter*, *Giardia lamblia*, enteroinvasive *Escherichia coli*, *Shigella* and *Yersinia*.

Early identification of clinical signs and symptoms of dehydration and hypovolemia is essential in the management of the HIV infected child presenting with diarrhea in the ED, especially if this is accompanied by vomiting or fever, so that early oral or intravenous rehydration can be initiated. When a bacterial etiology is suspected, empiric therapy with antibiotics should be implemented, either orally (cotrimoxazole) or intravenously (third generation cephalosporins) in case of intolerance or when an invasive disease is suspected. The etiologic diagnosis of diarrhea, although sometimes complex, is critical because it allows to start specific antibiotic treatment at an early stage. The higher risk of children with HIV infection to develop invasive infections

Table 2.19.3: Most common germs in infectious diarrhea in children infected with HIV

Virus	Bacteria	Opportunistic infections
Rotavirus	*Salmonella sp.*	Atypical mycobacteria
Enterovirus	*Shigella sp.*	*Giardia lamblia*
Adenovirus	*Campylobacter* sp.	*Cryptosporidium*
CMV	*Yersinia enterocolitica*	*Entamoeba hystolitica*
	Escherichia coli	*Microsporidia*
	Clostridium difficile	*Isospora belli*
	Vibrio cholerae	*Cyclospora*

secondary to diarrhea, especially by *Salmonella* and other enteroinvasive bacteria, should always be kept in mind.

Other non-infectious causes of diarrhea in children with HIV infection include lactose intolerance and, in the patient with advanced disease, malabsorption. Most antiretroviral drugs, and especially protease inhibitors, commonly cause gastrointestinal secondary effects (abdominal pain, nausea and vomiting, and watery diarrhea) during the first days or weeks of treatment (Table 2.19.4); these are usually mild and self-limited, although a switch to a different antiretroviral is seldom required.[10] In some patients, these HAART-related mild gastrointestinal symptoms (nausea or semiliquid stools) may persist for months. Other common causes of abdominal pain in the HIV infected child are: urinary tract infections, chronic constipation or lower lobe pneumonias.

Acute appendicitis is the most common cause of acute abdomen in pediatric patients infected with HIV. When facing clinical signs and symptoms consistent with an acute abdomen (progressive abdominal pain, vomiting, decreased peristalsis and signs of peritoneal irritation), the diagnostic evaluation should be early and aggressive, as a higher risk of perforation and evolution to peritonitis has been noted in these patients. Initial blood tests should include complete blood count and differential (although leukocytosis may not be observed initially), and liver (lactate dehydrogenase, alanine and aspartate aminotransferases, bilirubin and coagulation tests), kidney and pancreas functions. Abdominal computed tomography scan remains the preferred supplemental diagnostic tests for acute appendicitis.

The following two clinical conditions should always be kept in mind by the ED physician, because they often present with abdominal pain and are potentially fatal: the previously described abacavir hypersensitivity syndrome, and lactic acidosis associated with the use of nucleoside reverse transcriptase inhibitors (NRTIs), that presents with malaise, nausea and vomiting, abdominal pain, weakness or difficult breathing (Table 2.19.4).[10] The NRTIs inhibit both viral reverse transcriptase and human gamma-polymerase, an enzyme which is responsible for mitochondrial DNA replication. The depletion in mitochondrial DNA will ultimately lead to a dysfunction in the mitochondrial respiratory chain which may be clinically relevant.

Acute pancreatitis is generally diagnosed in children with advanced HIV disease as a result of the direct cytopathic effect of HIV on the gland, and because of other viral (*Cytomegalovirus*) or parasitic infections (*Cryptosporidium*). Treatment-related pancreatitis has also been described in the HIV infected patient, involving both several antiretroviral drugs (didanosine, lamivudine, stavudine, lopinavir-ritonavir, indinavir, saquinavir or ritonavir) and other antibiotics (pentamidine, isoniazid, azithromycin, clarithromycin or fluconazole).

Patients coinfected with Hepatitis C or B viruses[11] may undergo acute decompensated crisis of chronic liver disease, which generally manifest with ascites, right upper quadrant abdominal pain, elevations of aminotransferase levels above previously raised values, jaundice and dark urine, bleeding tendency, nausea and vomiting. Other causes of jaundice include cholecystitis (fever, right upper quadrant pain and chills) in patients with advanced disease and coinfection with *Cytomegalovirus* or *Cryptosporidium*, and acute hepatitis due to other viruses (Epstein-Barr virus, Hepatitis B or A viruses or Cytomegalovirus). In these cases, the abdominal ultrasound is the imaging diagnostic technique of choice in the ED.

Renal colic is a common complication of indinavir therapy (Table 2.19.4), a protease inhibitor currently not approved in the pediatric age. The differential diagnosis of an abdominal mass in the immunocompromised patient with abdominal pain includes a lymphoproliferative process and atypical mycobacteria or *Cytomegalovirus* infection. Gastrointestinal bleeding is uncommon in pediatric patients with HIV infection, generally involves the immunocompromised child and may be due to different etiologies: esophageal varices (upper bleeding), ulcerative CMV colitis (lower bleeding), coagulopathies or tumors of the digestive system.

Retrosternal pain may be the first symptom of candida esophagitis in children and adolescents with advanced HIV disease or severe immunosuppression. Candida esophagitis is often accompanied by dysphagia or odynophagia and, less often, fever. The presence of oral candidiasis points to the diagnosis, but the later is not always present. Esophagitis can also be due to herpes or *Cytomegalovirus* infection. The diagnosis usually requires the patient to undergo an esophagoscopy with mucosal biopsy. Initial treatment consists of analgesia, specific antibiotic therapy and nutritional support.

Skin Problems in the HIV Infected Child

The HIV infected child often presents to the ED with skin lesions. Some exanthematic diseases, such as herpes, chickenpox/zoster or scarlet fever, should be early recognized and parenterally treated, at least during the first hours or days of evolution. Toxicodermias caused by antiretroviral drugs but also by other antibiotics (i.e. sulfonamides) are also frequent (Table 2.19.4). Petechiae, purpura is common in patients with HIV related thrombocytopenia, typical feature of vertically acquired HIV infection, which shows increased morbidity in infants and in those patients affected with hemophilia as well.

Table 2.19.4: The most common antiretroviral-related adverse effects with acute or subacute presentations in the HIV infected child

Antiretroviral agent	*Adverse effect*	*Initial therapeutic management*
Indinavir	Renal colic because of renal precipitation of radiolucent indinavir crystals	Hydration and analgesics + temporary interruption of HAART (2-3 days)
Most protease inhibitors	Watery diarrhea, especially during the first 2 weeks of treatment. Usually self-limited	Supporting treatment; often not needed to stop HAART
Most antiretroviral drugs	Nausea and vomiting, especially during the first 2 weeks of treatment. Usually self-limited	Supporting treatment; often not needed to stop HAART
Abacavir	Hypersensitivity reaction in 2-5% of patients during the first month of treatment; it presents with abdominal pain, fever, exanthema, dyspnea, cough, pharyngitis and may be life-threatening	Immediate interruption of HAART and life support measures. Abacavir should never be reutilized
Nucleoside analogs, mainly stavudine and didanosine	Nonspecific syndrome consisting of fatigue, abdominal pain, tachypnea, anorexia, nausea and vomiting several months after initiating the drug, it progresses to lactic acidosis and death; concomitant liver failure is common. In infants, it may present with a neurologic syndrome (seizures, neurologic regression, pyramidal signs) together with hyperlactatemia	Immediate interruption of HAART and life support measures; use of cofactors and vitamin supplements is recommended
Didanosine and most protease inhibitors	Acute pancreatitis: severe abdominal pain, vomiting, fever Elevated lipase and amylase; amylase alone is often elevated due to HIV related parotid enlargement	Analgesics, NPO and parenteral nutrition; temporary interruption of HAART
Nevirapine, efavirenz, etravirina and nelfinavir	Toxicodermia that may progress, in some cases, to Stevens-Johnson syndrome, along the first weeks of treatment	In most patients, temporary interruption of HAART and use of antihistamine drugs is enough; usually safe to reinitiate the same drug
Efavirenz	Conduct disorders, sleep problems, hallucinations and other psychiatric manifestations in the first weeks of treatment	Administration of efavirenz at bedtime usually is enough; discontinuation rarely needed

Neurologic Problems in the HIV infected Child

HIV is a neurotropic virus. Neurologic manifestations associated with HIV infection in children are divided into those whose pathogenesis is related to the virus itself, and the secondary ones (opportunistic infections, neoplasms, cerebrovascular disease and those resulting from drug-related toxicity). In the natural history of vertically-acquired HIV infection, virtually all pediatric patients developed primary neurological disease to some degree (HIV related encephalopathy). This situation has radically changed since the implementation of HAART.[12] In any case, HIV related encephalopathy seldom presents in an acute manner and, therefore, does not usually motivate a consultation to the ED.

Currently, secondary pathologies of the central nervous system in the HIV infected child are rare when compared with the adult patient, and often occur in the context of severe immunosuppression.[13] Of note, stroke and undifferentiated primary lymphoma of the central nervous system are the most common causes of focal neurologic sign and brain mass in this group of patients, respectively. Undifferentiated primary lymphoma of the central nervous system is also less common in children than in adults, and may present subacutely with mood changes, altered level of consciousness, seizures or focal signs. It is usually located in the thalamus and basal ganglia, unlike brain metastases which are generally well-demarcated lesions located at the junction of gray and white matter. Patients with HIV infection may also present with stroke, generally consisting of acute focal signs (most often hemiparesis) and which are due to either ischemia (secondary to thrombosis or embolism) or hemorrhage (more frequent in patients with thrombocytopenia). The ischemic stroke is also associated with vasculitic lesions caused by HIV or other viruses, particularly varicella-zoster virus.

Other conditions that may acutely present with focal neurological signs or symptoms are cerebral toxoplasmosis, progressive multifocal leukoencephalopathy (due to JC virus infection), and herpes virus or CMV encephalitis,[11] although opportunistic infections are rare in the vertically-infected child, with the exception of those that are also transmitted from mother to child, such as congenital CMV infection or toxoplasmosis. Anyhow, it should be kept in mind that the most prevalent infection of the central nervous system in HIV infected pediatric patients is bacterial meningitis, caused by the same germs as that in the general pediatric population (*Pneumococcus, Meningococcus*, *Haemophilus influenzae*, *Salmonella sp.* or *Escherichia coli*).[14] Headache is also a common complaint in children with HIV infection and, besides other common etiologies, may be secondary to the exposure to some antiretroviral drugs, such as nevirapine or efavirenz.

The first diagnostic and therapeutic approach to the HIV infected child with neurologic complaints in the ED must include a thorough clinical examination and a fundoscopy to rule out intracranial hypertension. An adequate brain imaging technique (cerebral ultrasound in infants and/or computed tomography or magnetic resonance, sometimes with intravenous contrast) is mandatory before lumbar puncture when any of the following findings is present: seizures, focal sign in clinical examination, papilledema, altered mental status, any characteristic of malignant headache or any other suspicion of intracranial hypertension. When cerebrospinal fluid is obtained through a lumbar puncture, standard biochemical, cytochemical and microbiological tests should be performed, as well as other tests aimed to identify some opportunistic infection (molecular microbiology techniques for Herpes virus family or mycobacteria, fungal cultures and India ink stain for the detection of Cryptococcus).

Cardiorespiratory Problems in the HIV Infected Child

Respiratory tract infections due to common germs are, without a doubt, the most frequent cause of respiratory distress in the pediatric patient with HIV infection (virus-induced wheezing, and pneumococcal or other bacterial pneumonia). Although they usually follow a benign course and resolve with standard therapy, it is also true that they may also lead to more serious or prolonged symptoms in the immunocompromised child. Similarly, viral pneumonitis with severe hypoxemia (in the setting of varicella-zoster virus or CMV infection) or local suppurative complications or bacteremia after bacterial pneumonia may arise in this group of patients.

Among chronic respiratory disorders in pediatric HIV infection, lymphoid interstitial pneumonia (LIP) is the most prevalent.[15] LIP is considered to be pathognomonic of pediatric HIV infection and constitutes a diagnostic criterion of AIDS. LIP is the result of a diffuse inflammatory infiltrate of the alveolar septa and surrounding lymph vessels by CD8 T-lymphocytes, plasma cells and histiocytes. Although LIP very rarely presents acutely, its high prevalence and clinical and radiological characteristics may be misleading when assessing the patient with respiratory symptoms in the ED. LIP usually develops after one year of age, unlike *Pneumocystis jirovecii* pneumonia, that typically affects infants aged less than 12 months. Early LIP is characterized by the presence of pulmonary infiltrates on chest X-ray (fine reticulonodular unspecific pattern in lower pulmonary lobes,

accompanied by hilar lymphadenopathy), generally without significant signs or symptoms. Respiratory symptoms insidiously develop along the first to 5 years of life (mild cough and progressive fatigue and dyspnea/tachypnea) with normal clinical examination; this clinical picture may worsen following a respiratory banal infection.

Pneumocystis jirovecii pneumonia (PCP) is an opportunistic infection and the most prevalent AIDS-defining criterion among vertically-HIV infected patients.[11] PCP incidence rate reaches its peak in the first year of life, especially between 3 and 6 months of age, with no seasonal influence, as it has been described in adults. The risk of developing PCP is higher in the immunosuppressed infant, but it has also been described in patients with normal CD4 cell percentages. PCP usually presents abruptly with high fever (up to 40°C), cough, dyspnea, tachypnea, and cyanosis within hours after the onset of symptoms. Clinical examination shows a seriously ill child with respiratory distress and cyanosis. In older children, the onset may be more insidious and fever is less common; however, the rest of respiratory symptoms should suggest the diagnosis. Children affected with PCP show severe hypoxemia, which often requires intubation and ventilatory support. An elevated serum lactate dehydrogenase is observed in 50 percent of the patients. PCP-related morbidity and mortality in HIV infected infants are high, in spite of the implementation of appropriate therapies. Early diagnosis of PCP requires a high degree of clinical suspicion. The initial chest X-ray usually shows some nonspecific diffuse interstitial infiltrates wihout hilar lymphadenopathy, although all kinds of radiologic patterns have been described. The differential diagnosis of PCP includes viral pneumonitis (such as those due to respiratory syncytial virus, parainfluenza virus, CMV or Epstein-Barr virus), mycobacterial infections or LIP. The diagnosis can be definitively confirmed by histological identification of the organism in sputum or bronchioalveolar lavage. When PCP is clinically suspected, early implementation of intravenous antibiotic is mandatory; the drug of choice is trimethoprim sulfamethoxazole, pentamidine being the second option. In children with hypoxemia (pO_2 <70 mm Hg), intravenous prednisone should be added.

Tuberculosis (TB) in children manifests as a pulmonary infection with high risk of progression and hematogenous spread (extrapulmonary disease: meningitis, disseminated infection, lymph node involvement) and, therefore, requires early diagnosis and treatment. The increased survival of HIV infected pediatric patients after the implementation of HAART and the fact that TB remains highly prevalent in many regions in the world should keep ED physicians alert. TB should always be ruled out when prolonged fever with or without respiratory symptoms (cough, tachypnea, etc) occurs. The radiologic findings are nonspecific, the reticulonodular pattern being the most frequent; the images of cavitation of the lung parenchyma are rare in childhood. Main differential diagnosis for pulmonary TB are PCP and LIP. Extrapulmonary disease will facilitate the diagnosis. The initiation of TB prophylaxis or TB treatment is never a medical emergency. The peculiarities of the patient with HIV infection: the increasing prevalence of strains of *Mycobacterium tuberculosis* with resistance to some antituberculous drugs, the multiple interactions between some antiretrovirals and some antituberculous drugs, and the need to ensure good compliance and tolerance to treatments, advise to defer the initiation of these regimens until the consultant in pediatric infectious diseases is available.

Myocardial involvement (myocardiopathy) may occur in children with HIV infection. It was first described in association with the use of high dose zidovudine, but it has also been reported in untreated patients, thought to be due to the cytopathic effect of HIV and other viruses (adenovirus, echovirus or CMV) in the cardiac muscle. In general, patients do not present with acute symptoms, but may complain of dyspnea without pulmonary disease, syncope, profuse sweating, peripheral edema, hepatomegaly, and other symptoms secondary to heart failure.

Finally, an increased incidence of cardiovascular and cerebrovascular events (ischemic heart disease, stroke, etc.) has been reported in the HIV infected adult patient, which have been both associated to classic risk factors but also to HIV infection and exposure to HAART and its toxicity.[16] Thus, in the adolescent complaining of symptoms consistent with ischemic heart disease or stroke, especially when several risk factors converge (prolonged use of HAART, dyslipidemia, decreased insulin sensitivity, smoking, etc.), the diagnostic tests to early identify or rule out these conditions should be performed in the ED.

Other Opportunistic Infections in the Emergency Department[11]

Mycobacterium Avium Complex (MAC) Disease

In immunocompetent patients, the most frequent presentation of MAC infection is lung disease, followed by lymphadenitis; the disseminated form is extremely rare. The latter is the most common presentation in immunosuppressed HIV infected patients (with CD4 cell counts below 100/mm^3) and is characterized by prolonged fever, night sweats, malaise and weight loss. MAC disease is associated with high morbidity and mortality in patients infected with HIV. These patients usually show anemia and elevated alkaline phosphatase levels as well. Some

children may complain of digestive symptoms such as chronic diarrhea, abdominal pain, colitis, or malabsorption; lymphadenopathy and hepatosplenomegaly with normal liver enzymes are also common. Cholestasis due to extrahepatic biliary obstruction secondary to periportal lymphadenopathies has been reported as well. Because bacteremia is common in patients with disseminated MAC infection, obtaining two blood cultures on special media is generally enough to reach the diagnosis. The differential diagnosis should be made with other conditions that lead to digestive symptoms and prolonged fever, such as lymphoma, salmonellosis, cryptosporidium, CMV, etc.

Herpes Simplex Virus (HSV) Infection

While primary infections caused by HSV types 1 and 2 are usually asymptomatic or mildly symptomatic (affecting skin and mucous membranes) in immunocompetent hosts, systemic involvement may occur in the immunocompromised patient. Similarly, the reactivation of latent infection is more common in the immunocompromised child. As a rule, the frequency and severity of HSV primary infection and relapses in HIV infected children are inversely proportional to the degree of immune suppression. Herpetic gingivostomatitis (usually caused by HSV type 1) relapses in 5 to 10 percent of children with HIV infection and may spread to esophagus, skin and other organs. Pharyngitis in the context of a primary infection by HSV type 2 is very painful and is accompanied by significant impairment of general condition. Genital infection is usually caused by HSV type 2 in sexually active people. It is usually asymptomatic, although the presence of mucosal lesions in the genital and perirectal regions may cause dysuria, vaginal or urethral pain, fever and painful regional lymphadenitis; abdominal pain or aseptic meningitis have also been described. HSV type 2 proctitis may present with tenesmus, constipation, sacral paresthesias or urinary retention. Relapses are usually milder in its evolution.

Herpetic meningoencephalitis is a life-threatening condition that requires early and aggressive treatment. It has classically been described with an hemorrhagic cerebrospinal fluid and the involvement of the temporal lobes in the electroencephalogram and neuroimaging. The differential diagnosis of this condition is broad and includes other viral infections (HIV itself, CMV, or varicella-zoster virus), brain abscess, tuberculous meningitis, toxoplasmosis, cryptococcal and other fungal meningitis, and also noninfectious conditions, such as cerebrovascular accidents or neoplasms. Herpetic esophagitis presents with fever, retrosternal pain, odynophagia and usually, but not always, typical oropharyngeal lesions. Its main differential diagnosis are candida and CMV esophagitis. Esophagoscopic mucosal biopsy is usually needed to reach an accurate diagnosis. Disseminated herpes infection (by HSV types 1 or 2) is the most severe clinical form of the disease in the immunocompromised patient. A generalized skin rash is present, with vesicles coalescing into hemorrhagic bullae, together with hepatic, renal, adrenal, lung and/or central nervous system involvement. The patient presents with fever, hepatitis, pneumonia, shock, hemorrhage, disseminated intravascular coagulation, seizures and/or kidney failure, and may progress to death within days or weeks, not always showing a significant response to treatment.

The presumptive diagnosis of herpetic disease in the ED is based on the identification of typical mucocutaneous lesions, that may not be so typical in the immunocompromised host; HSV infections in the HIV infected patient may present with deep necrotic ulcers, with bleeding skin lesions or with an hyperkeratotic rash. Acyclovir is the treatment of choice for HSV disease. While oral acyclovir is preferred in most cases, intravenous treatment is initially required in moderate to severe disease, infection of the central nervous system, neonates and HIV infected children.

Varicella-Zoster Virus (VZV) Infection

In the HIV infected child, chickenpox may show a progressive and chronic evolution. The lesions are most numerous (over 400 per m^2 of body surface area), continue to emerge after the second week of illness (longer shedding), sometimes for months, and complications are more frequent, severe and lifethreatening in some cases. In the absence of specific treatment, the immunocompromised HIV infected patient may develop viral pneumonitis, central nervous system involvement (acute cerebellar ataxia, aseptic meningitis, encephalitis or fulminant cerebral vasculitis), hepatitis or other visceral complications, but also skin superinfections and osteomyelitis, with risk of bacteremia and sepsis. Similarly, zoster may arise within few months after primary infection, and may affect multiple dermatomes or even progress to a disseminated rash with visceral involvement, causing similar complications to those of chickenpox. Zoster can show a chronic or recurrent evolution as well.

As in HSV disease, the presumptive diagnosis of the HIV infected child with VZV infections in the ED may be complicated by atypical lesions (necrotic, ulcerated, hyperkeratotic or bleeding skin lesions). Differential diagnosis for VZV infection include impetigo, HSV disease, atypical measles, insect bites and scabies. In the ED, intravenous acyclovir is initially recommended in all HIV infected children with chickenpox or zoster.

Postexposure prophylaxis: Hyperimmune immunoglo-bulin should be administered within 96 hours after contact with the index case to those immunocompetent

patients with HIV infection who have not had chickenpox or have not been vaccinated previously or, in immuno depressed children, regardless of their serologic status. In the absence of hyperimmune immunoglobulin, polyvalent immunoglobulin can be used (250-400 mg per kg of body weight, intravenously).

Cytomegalovirus (CMV) Infection

CMV infection is one of the most common coinfection in HIV infected patients. Congenital CMV infection does not differ clinically from that of HIV negative healthy infants, although a more aggressive evolution is common. Acquired primary CMV infection is usually non-symptomatic or, in some cases, presents with a mononuclear syndrome or a nonspecific febrile syndrome. The immunocompromised patient is at increased risk of developing a symptomatic primary infection. In the HIV infected child, reactivation of latent CMV infection remains the most frequent presentation of CMV coinfection, especially following congenital infection. Reactivation of latent CMV infection usually occurs together with severe cellular immunosuppression (less than 50-100 CD4 cells/mm^3) and associates a wide spectrum of clinical manifestations: pneumonitis, gastritis, colitis, encephalitis, pancreatitis, leukopenia, myelopathy, neuritis, hepatitis, lymphadenopathy and usually a febrile syndrome.

Although CMV can be the one responsible for pneumonitis in immunocompromised patients, it is often isolated together with other pathogens (*Chlamydia*, *Mycoplasma*, *fungi* or *Pneumocystis jirovecii*) in bronchoalveolar aspirates from immunosuppressed patients. An empiric broad spectrum antibiotic therapy is recommended in these patients in the ED, until microbiological results are available. CMV infection leads to extensive gastrointestinal involvement, mainly colitis, interfering with feeding and promoting the deterioration of nutritional status. Patients usually present with vomiting, bloody diarrhea, abdominal pain, weight loss, malabsorption, hepatosplenomegaly and laboratory abnormalities such as anemia, leukopenia and elevated transaminases. CMV retinitis shows a very rapid progression to blindness, early diagnosis and treatment remaining essential to prevent this evolution. CMV also causes meningitis and meningoencephalitis, clinically indistinguishable from those produced by other viruses.

Diagnosis of CMV disease generally requires histologic confirmation, which is not always feasible. Diagnosis of CMV infection requires isolation of the virus (antigen detection, viral culture or genome detection); the quantification of CMV viral load in plasma has been correlated with disease risk and treatment response. Serological tests are useless in patients with HIV infection and suspected CMV disease. None of these are usually available in the ED and, therefore, the empirical initiation of intravenous ganciclovir is recommended when CMV disease is suspected in the immunodeficient HIV infected child. In the adult patient, oral valganciclovir (a ganciclovir prodrug that is metabolized in the intestine and shows a good bioavailability) could be useful in treating mild forms of disease or as a maintenance therapy; studies with this drug in the pediatric age are ongoing. Other active drugs against CMV are foscarnet or cidofovir.

Candida Infection

Asymptomatic Candida colonization affects most infants from the age of 4 weeks. Candidal dermatitis or thrush are common diseases in healthy infants. In immuno-compromised patients, mucocutaneous and oropharyngeal candidiasis are frequent, and the latter may extend to the esophagus or larynx, occasionally leading to fungemia and disseminated candidiasis. Oropharyngeal candidiasis occurs in 15-40 percent of children with HIV infection, recurrences being common when CD4 cell count is low. Four major types of oropharyngeal candidiasis are recognized: (1) **Pseudomembranous** (the most frequent) white patches on the tongue, pharynx, gums and oral mucosa that are easily released; (2) **Hyperplastic** white plaques which cannot be removed by scraping; (3) **Erythematous or atrophic** spotty red areas on the cheek mucosa, the palate and dorsum of the tongue; and (4) **Angular cheilitis** cracks radiating from the angles of the mouth, often associated with small white plaques.

Esophageal candidiasis is usually associated with oral candidiasis, but not in all cases. The patient presents with retrosternal pain, dysphagia and odynophagia, of variable severity. Again, the diagnosis in the ED is based on clinical suspicion and needs endoscopy for confirmation (diffuse raised white plaques that characteristically can be removed from the mucosa). Systemic candidiasis (mainly caused by *Candida albicans* and *Candida tropicalis*) is infrequent and generally associated with predisposing factors such as chronic oropharyngeal candidiasis, intravenous catheters, parenteral nutrition, broad-spectrum antibiotic treatment and neutropenia. Visceral involvement may occur in up to 20 percent of patients, including renal or hepatosplenic candidiasis, fungal pneumonia, candida osteomyelitis, endophthalmitis, etc.

As a rule, topical nystatin or miconazole are of little use in the HIV infected child with thrush, but can be used in initial episodes. Oral fluconazole, rather than ketoconazole or itraconazole, is generally preferred in oropharyngeal candidiasis, although recurrences are common, especially in the absence of an effective HAART. In patients with persistent thrush, in moderate to severe cases or when esophagitis is suspected, intravenous

amphotericin B is the treatment of choice, as it is in systemic candidiasis. Lipid formulations of amphotericin B allow the administration of this drug at high doses from the start of treatment, with less renal and bone marrow toxicity. The experience with voriconazole and echinocandins in HIV infected children is still scarce.

Cryptosporidium Infection

Cryptosporidium parvum, a parasite with worldwide endemic distribution, is considered to be responsible for approximately 20 percent of episodes of diarrhea in patients with AIDS. Crypstosporidiosis produces a bout of watery diarrhea, sometimes associated with nausea and vomiting, mild fever, abdominal pain, weight loss, anorexia, malaise, and flatulence. The infection usually goes away within a week or two in immunocompetent patients, but may be longer and life-threatening in the HIV infected patient, in whom cholecystitis, sclerosing cholangitis, pancreatitis, hepatitis, and even pulmonary involvement have also been reported.

Diagnosis is based on the identification of the parasite in stool samples by a modification of the Ziehl-Neelsen stain: the Kinyoun stain. No specific treatment for cryptosporidiosis is available. In the ED, proper hydration and avoidance of stimulating beverages, gluten and fat should be assured. Paromomycin and azithromycin have been used both in children and adults with variable results. Some patients require inhibitors of intestinal motility (loperamide, opiates or somatostatin analogs) due to the large volume of fecal losses.

Toxoplasmosis

Cerebral toxoplasmosis is the most frequent opportunistic infection of the central nervous system and also the most common cause of focal neurologic signs in adults infected with HIV. Because it generally represents the reactivation of a latent infection following immunosuppression, it is much less common in childhood. Clinical presentation of cerebral toxoplasmosis depends on the affected area in the brain. It generally presents subacutely with headache, altered mental status (confusion, lethargy or coma) and focal neurologic signs, most often hemiparesis or hemiplegia, hemianesthesia, aphasia, ataxia, visual field disturbances, dysmetria, tremor, hemiballism, or choreoathetosis. Seizures may also occur at disease onset. Other less common manifestations include panhypopituitarism, syndrome of inappropriate antidiuretic hormone hypersecretion, hydrocephalus, dementia, toxoplasmosis encephalitis, transverse myelitis and conus medullaris syndrome. Toxoplasma retinochoroiditis in adult patients with AIDS is uncommon and usually presents together with cerebral involvement. On the contrary, fundoscopy is mandatory in all HIV infected children because Toxoplasma retinitis is the most frequent presentation of congenital toxoplasmosis and may also represent a focus of reactivation with advancing immunosuppression.

In the ED, serologic tests are almost useless for the diagnosis of toxoplasma disease in HIV infected children beyond the neonatal age. Recent techniques that allow the detection of toxoplasma genetic material in blood or cerebrospinal fluid are usually not available in the ED. Again, the presumptive diagnosis of cerebral toxoplasmosis will be based on clinical suspicion and the neuroimaging findings. Brain scan generally shows single or multiple round hypodense lesions with edema and mass effect, located in the basal ganglia or the cortico-medullary junction; ring-enhancing lesions are typically observed on postcontrast studies. If available, magnetic resonance imaging is considered the most sensitive imaging modality to study brain lesions in the HIV infected patient. The differential diagnosis of cerebral toxoplasmosis should be made mainly with primary central nervous system lymphoma and progressive multifocal leukoencephalopathy.

Treatment of toxoplasmosis consists of pyrimethamine plus sulfadiazine and folinic acid. Corticosteroids are recommended for children with central nervous system disease when cerebrospinal fluid protein is highly elevated (i.e, >1000 mg/dl) or with focal lesions with substantial mass effects.

Antiretroviral Drug Related Problems in the Emergency Department[10]

At present, most pediatric patients with HIV infection receive highly active antiretroviral combination therapies (HAART) in order to control viral replication, maintain normal immune function and avoid the development of AIDS. In 2008, the CHER trial[17] provided definite evidence supporting early HAART in vertically-HIV infected pediatric patients, and implementing combined antiretroviral therapy is now recommended in all infants diagnosed with HIV infection before the age of 1 year.[10] HAART has dramatically reduced morbidity and mortality from HIV infection/AIDS, but it is also true that these long-life treatments have been associated with numerous adverse effects. The most common antiretroviral-related adverse effects with acute or subacute presentations are summarized in Table 2.19.4.

Another dilemma in HIV infected children is whether to continue the usual antiretroviral treatment when an unexpected acute disease that makes compliance difficult occurs. As far as it is reasonably possible, maintaining HAART is recommended, since optimal adherence to treatment is essential for its efficacy. When HAART interruption is needed (gastric intolerance, need for surgery), all drugs should be stopped at once. If the

HAART regimen includes a nonnucleoside reverse transcriptase inhibitor (nevirapine, efavirenz or etravirine), to the extent possible, the latter should be discontinued 1 to 2 weeks before interrupting the rest of the treatment. Non nucleoside reverse transcriptase inhibitors have a longer plasma half-life than other antiretrovirals and the interruption of all HAART at the same time leads to functional monotherapy, with the risk of developing viral mutations associated with resistance to these drugs.

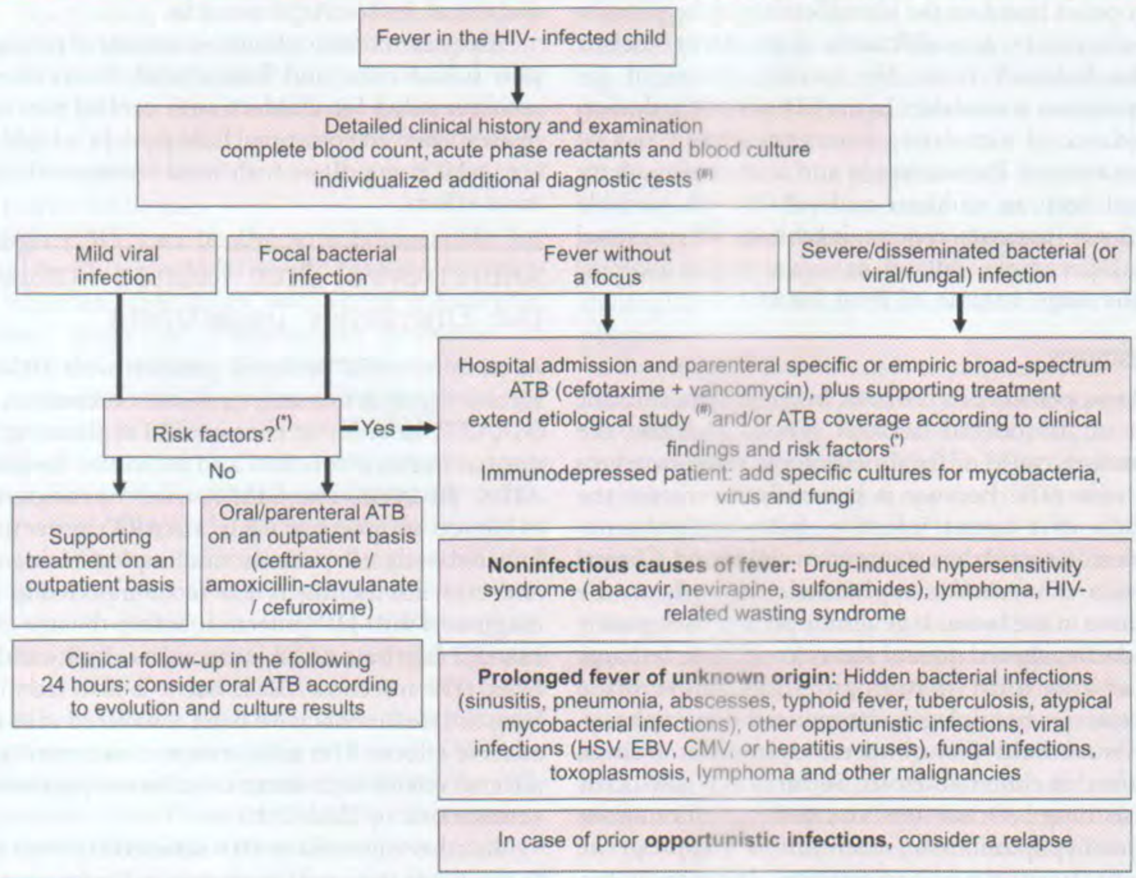
Case Studies

Case 1

A 4-month-old male infant presented to his local ED with a 4-day history of respiratory difficulty and fever. He had been diagnosed with vertically-transmitted HIV infection at the age of 3 months, when the patient was started on combined antiretroviral therapy (zidovudine plus lamivudine plus nevirapine). Despite suboptimal adherence to HAART because of vomiting, the *plasmatic* viral load had dramatically decreased from 5.6 log copies/ml at diagnosis to 3.1 log one month later. His CD4 cell percentages were always within normal ranges (nadir CD4 cell percentage: 28%); primary PCP prophylaxis had not been initiated yet. The rest of his medical history was unremarkable.

At presentation, the patient presented moderate respiratory distress, hypoxemia (hemoglobin oxygen saturation 90% on room air), and coarse breath sounds bilaterally. Syndromic diagnosis was respiratory distress in the setting of a lower respiratory tract infection. The initial chest radiograph showed bilateral lower lobe infiltrates and hyperinflation. Laboratory results on admission included leukocytosis and elevated C reactive protein. In this patient, initial differential diagnosis included mainly bacterial pneumonia, viral bronchiolitis and PCP. Rapid tests on nasopharyngeal swab

Algorithm 1. Initial diagnostic and therapeutic management of HIV infected pediatric patients presenting with fever



Chest X-ray, urinalysis, spinal tap, tuberculin test, computed tomography of the sinus, abdominal ultrasonography, blood and other body fluid cultures for common bacteria, mycobacteria, fungi and viruses, throat swab, detection of cryptococcal antigen, genome detection for different germs by means of polymerase chain reaction techniques, funduscopy (CMV or toxoplasma chorioretinitis), liver biochemistry and bone marrow aspiration study.

* Current or previous clinical diseases or immune situation consistent with AIDS, laboratory evidence of bacterial infection (leukocytosis or leukopenia, a left shift, elevated inflammatory markers), prior severe bacterial infections, maximum temperature over 39ºC, infants below 12 months of age, patients without HAART, neutropenia or other primary or secondary causes of immune deficiency, and patients with central venous catheters.

samples were negative for influenza A and B and respiratory syncytial virus. Intravenous cefotaxime was implemented, together with nebulized albuterol, oxygen supplement- ation, fluids and general care. Despite this, his condition worsened in 36 hours, with severe respiratory distress and increasing hypoxemia. Chest X-ray demonstrated worsening pulmonary infiltrates as well. A presumptive diagnosis of PCP was done and intravenous therapy with trimethoprim/ sulfamethoxazole and methylprednisolone were initiated. Lactate dehydrogenase levels were found to be elevated. The patient was transferred to the PICU, where mechanical ventilation was implemented because of respiratory failure. Gomori methenamine silver stain on bronchoalveolar lavage sample confirmed PCP. Progressive clinical improvement occurred and a 21-day course of trimethoprim/ sulfamethoxazole was completed. Thereafter, the patient received secondary prophylaxis for PCP.

Key Points

- Confirmed or presumptive PCP is the most common AIDS-defining disease in HIV infected children worldwide, and is associated with high mortality rates.
- The differential diagnosis of PCP includes bacterial and viral pneumonia, but also mycobacterial infections and LIP; coinfection with *Cytomegalovirus* is common in severely immunosuppressed patients.
- A high index of clinical suspicion is needed to reach an early diagnosis and implementation of intravenous trimethoprim/sulfamethoxazole, usually before microbiologic confirmation.
- In the HIV infected infant, PCP may present even with normal CD4 percentages.

Case 2

A 3-year-old white male presented to the ED with perioral rash. He had been seen 24 hours earlier for complaints of poor feeding and fever (up to 40ºC) with clinical signs of upper respiratory tract infection on physical examination. He was treated with antipyretics and discharged without incident.

The following day he was noted to have a perioral petechial rash with persistence of fever and increasing malaise. Intravenous fluid was initiated and he was transferred to the PICU under the suspicion of meningococcal sepsis. Family history was unremarkable and immunizations were complete. Regarding medical history, the patient had presented recurrent otitis media and was being studied because of failure to thrive and persistent diarrhea during the last 6 months.

On admission, the infant appeared severely ill, with prolonged capillary refill, respiratory rate 41/min, pulse rate 176/min and undetectable blood pressure. He showed a rigid neck. Small, nonblanching, red macules were initially located on the upper lip, nose and ears. In two hours, they rapidly progressed to a diffuse petechial and purpuric rash over the limbs, with great confluent lesions around both knees and elbows, that were less prominent distally. The remainder of the physical examination was unremarkable.

Blood cultures were obtained and intravenous cefotaxime and vancomycin were initiated. Laboratory examination revealed: normal red and white blood cell count; platelet count, 26000/mm^3; C-reactive protein 155 mg/l; prothrombin time 23 sec (normal range = 10.2-12.2 sec); and activated partial thromboplastin time 53 sec (normal range = 25-35 sec). Coagulopathy and thrombocytopenia made immediate lumbar puncture unadvisable. Chest radiograph and urine analysis were normal. The patient was managed with mechanical ventilation, intravenous fluids, multiple blood product transfusions and inotropic support with good clinical evolution. At 72 hours, blood cultures grew *Neisseria meningitidis*. Three days after presentation, lumbar puncture was consistent with meningitis. He was discharged from the PICU after 10 days. A later immunologic evaluation revealed positive serology for HIV, that was further confirmed with positive plasmatic RNA HIV. HIV infection was as well confirmed in his mother.

Key Points

- Clinical features of bacterial infections in HIV infected children are usually similar to those of HIV uninfected patients, although they occur more often and are more severe.
- Consequently, the diagnostic and therapeutic management of bacterial infections in HIV infected children is also similar to that of the healthy patient.
- Physicians in the ED must be familiar with historical factors, physical examination findings, and laboratory and radiologic abnormalities that may put a child at risk for HIV infection.

Key Messages

- ☞ The diagnostic evaluation of an HIV infected child in the Emergency Department begins with a thorough medical history and physical examination, and necessarily includes character and duration of symptoms, HIV disease status, recent exposures to ill persons, and signs of focal infection/inflammation.
- ☞ Fever in the HIV infected child may be due to focal infection, fever without a source, fever of unknown origin, HIV associated opportunistic infections, or malignancy. Focal bacterial infection and bacteremia rates are increased among HIV infected children.
- ☞ Besides fever, several other life threatening conditions may develop acutely in the HIV infected child and require early recognition and treatment, including respiratory distress, gastrointestinal bleeding, seizures and altered level of consciousness, and some antiretroviral-related adverse effects.

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SECTION III

Woman, Newborn and HIV

3.1

A Guide to the Clinical Care of Pregnant Women with HIV

Jyoti Dhar

Background

The introduction of highly active antiretroviral therapy (HAART) in women with HIV has led to women living longer in good health, with the possibility of pregnancy and very low risks of vertical transmission. HIV vertical transmission can occur during pregnancy, labor and delivery or with breastfeeding. The recommendation of HIV testing women in pregnancy, as part of routine antenatal care, is to introduce interventions that not only prevent mother-to-child transmission (MTCT) but also improve maternal health. A recent audit in England of 87 cases of perinatal HIV transmission demonstrated that 54 (62%) infants were born to women who were undiagnosed prior to delivery (half of these women also had refused HIV testing). 20 percent of the 54 infected infants were born of mothers who HIV seroconverted during pregnancy.[1]

In this chapter, we will discuss the wide range of clinical issues encountered and provide suggestions on the appropriate management of HIV positive women during pregnancy. We will also discuss, the challenges faced by healthcare professionals responsible for service provision, with emphasis on recognizing family, emotional and healthcare needs of pregnant HIV positive women except MTCT, which will be discussed in another chapter.

Epidemiology of HIV in Pregnancy

It has been recognized that women in the developing world are at higher risk of HIV infection due to a biological and sociological susceptibility and in some countries, HIV is a common complication in pregnancy. Furthermore, studies from India have demonstrated epidemics of HIV in different geographical settings and among people with different types of risk.[2,3] Current data suggests that sexual transmission, especially unprotected heterosexual transmission, is responsible in 84.6 percent of cases, infected needles and syringes in 6.78 percent, perinatal infection in 2.72 percent, unsafe blood and blood products in 2.57 percent and unspecified causes in 2.24 percent. Women, especially in rural areas, now account for 39 percent of all adult infection. Increasingly it is being recognized that married men in India act as 'bridge populations' in transmission, between the vulnerable and general populations.[4]

The average HIV prevalence among women attending antenatal clinics in India has been reported as 0.48 percent.[4] This is probably an underestimate as other studies indicate background reported seroprevalence rates of 13 to 24 percent among female STD clinic patients (in those who did not report themselves to be selling sex)[5] and HIV infection rates of between 6 to 85 percent in wives of HIV infected drug users and STI clinic patients.[6,7] The seropositivity rate among pregnant women in selected sentinel sites ranges between zero and over 2 percent in the states of Maharashtra and Karnataka, and as high as 6 percent in some slums in Mumbai.[8,9] Areas reporting HIV prevalence rates of zero in antenatal clinics may reflect a reporting bias, i.e. if the figures are derived from sources other than antenatal clinics, e.g. STD clinics.[10] Also, in some states and territories, under-reporting is common, as the antenatal prevalence rate is based on estimates from only a small number of clinics.[11]

Pregnancy and Risks of Transmission

The risk of MTCT in undiagnosed/untreated women is between 15 to 20 percent in non breastfeeding women in developed countries and 40 percent in breastfeeding women in resource limited settings.[12] In the absence of breastfeeding, two-thirds of transmissions occur intrapartum and one-third *in utero*. The most important predictor for transmission appears to be maternal plasma HIV RNA levels with no neonatal transmissions occurring at viral loads < 1000 copies per ml, though there is no

clear threshold above which all women transmitted the virus.[13]

The risk of MTCT in diagnosed/treated women is between 1 to 2 percent in developed countries with transmission rates <1 percent for non breastfeeding women on HAART, where the plasma viral load is undetectable at delivery.[14,15] There is a linear correlation between the mother's viral load and risk of transmission, though rare transmission has been reported in cases with viral load <50 copies at delivery.

Diagnosing HIV during Pregnancy

HIV Testing Issues

Testing Guidelines: Recommend routine prenatal HIV screening in the first trimester of pregnancy. If negative, repeat HIV testing in the third trimester of pregnancy needs to be considered in high prevalence areas, women at high risk of infection and in those with symptoms suggestive of acute HIV infection. Repeat testing is further supported by a recent study from Swaziland in pregnant women that showed an incidence rate of 16.75 per 1000 person years during pregnancy with 4.4 percent of women HIV positive at delivery when they had tested negative at initial testing (Keifer 2010).

HIV testing kits that are currently recommended for use in pregnant women are the fourth generation HIV antibody assays as they will test for both HIV antibody and p24 antigen. This testing method, besides reducing the diagnostic window period to 1 month (compared to the 3 month window) has excellent sensitivity (99.8 to 100%) and specificity (99.5 to 99.9%). A positive test will require further confirmation on the sample followed by repeating the test on a second sample.[16]

Point of Care tests (POCT) or Rapid HIV tests using finger prick blood or mouth swabs are currently in use especially in labor wards. Though they deliver results within 30 minutes of the test being taken, most of the currently available kits test for HIV antibody only (not p24 antigen) and hence a nonreactive result will fail to detect seroconversion in a high risk pregnant female. A reactive result, however, with this method will need further confirmation by your local laboratory.

Recommendation: HIV antibody testing to be considered in clinical practice and POCT for use in clinical situations where a rapid diagnosis will affect the immediate management of the patient, as in labor.

Psychosocial Issues

HIV diagnosis during pregnancy may be a profoundly shocking and life-changing event for the newly diagnosed HIV positive woman. Women are often blamed incorrectly as the source of HIV infection and may have to carry the dual burden of infection and of caring for infected family members. An early assessment of their social circumstances is therefore, essential. There may be a complex mix of emotional, psychosocial relationship, economic and even legal issues that arise directly out of the HIV diagnosis. In a study on psychosocial aspects, issues around health, treatment and fear of death were the major concerns expressed by 42 percent of women at first contact postdiagnosis, these becoming noticeably less significant (28%) at most recent contact.[17]

The newly diagnosed woman has a relatively brief time to make appropriate informed decisions that affect her own long term health and that of her fetus and her male partner.[18] As the success/failure of MTCT transmission is determined solely by the willingness of the woman to engage with healthcare professionals, in a number of cases this may lead to an inability to achieve the desired results. In such cases, support from a multidisciplinary team is crucial with the pediatrician taking the lead, acting on behalf of the unborn child. Informing the mother and seeking legal permission to treat the child after birth with antiretroviral drugs and preventing breastfeeding may also have to be considered.

Recommendation: An early assessment of the woman's circumstances, especially in those diagnosed in the antenatal setting.

Health Seeking Behavior Issues

There are many features that make this a challenging group to manage. Health data available from India on the proportion of symptomatic women seeking reproductive care suggests considerable variability, ranging from a minority to a majority in different studies.[19,20] For example, women in rural Tamil Nadu waited, on average, for a month before seeking any treatment.[20,21]

Communication between partners on sexual matters, including morbidity, is often restricted. Women are often, as noted by Ramasubban, "too afraid and confused to bring this (symptoms) to the notice of the family..., both because they are not supposed to have such problems in the first place and also because they are socially deemed to be polluters, the originators of sexual problems".[22] Spouses frequently do not inform their partners about their genital symptoms; a study among married women and men in rural Tamil Nadu reported that only slightly more than one-third (37.3%) of women with symptoms of possible reproductive tract infections, and one fifth (19.9%) of symptomatic male respondents informed their spouses about their illness experience.[23,24] Moreover, communication was generally indirect, using symbolic expressions and gestures, thus leaving "informed" spouses to guess about their partners' illnesses.

Confidentiality also may be an issue. It is important that the woman at all times is reassured this will be maintained. All HIV positive pregnant women should be encouraged to disclose their status to their partner /spouse and be involved in decision making. Often stigma and relationship concerns that remain fairly constant over time have been reported in this group, further limiting access to social support avenues within family networks and relying heavily on hospital or voluntary services.

Disclosure of HIV status may be a major concern initially but this lessens over time and should remain a key area in counseling. This is often a factor that determines the ability to gather social or family support. Family issues also must not be overlooked, as a number of these women are mothers with dependent children,[17] and testing these children for HIV may in itself be traumatic. Studies have shown that testing children born before their mother's HIV diagnosis is usually not a priority for many newly HIV diagnosed women. It is thus quite clear that due to a lack of evidence on which to base decisions, a pluralistic and often unregulated health sector and a highly vulnerable population, management of such patients can be fraught with difficulties.

Recommendation: Women receiving antenatal care need to be reassured that their confidentiality will be maintained and while disclosing results to spouse/ partner and testing previous children should be encouraged, it can be delayed till she is ready. At the same time, the antenatal team needs to ensure that results are clearly documented and communicated to the people involved in her management.

Sexual Abuse in Pregnancy

There has been only one previous longitudinal study of sexual violence with incident STI among pregnant women that found a two fold increased odds of incident STI with a history of sexual abuse.

The findings of high risk among married women reporting spousal sexual abuse suggests that healthcare professionals treating sexually transmitted diseases and HIV need to be aware of possible sexual violence, and ensure that patients are screened and provided with the necessary support. Reproductive health clinics can provide a necessary entry point for women who experience violence to seek counseling, education, care, and perhaps protection.[25]

Recommendation: Consider repeat HIV testing in the pregnant woman even if initial blood tests are HIV negative and on-going high risk is identified.

Effect of HIV Infection on Pregnancy

HIV infection should not mark the end of childbearing and a consistent number of women proceed to pregnancy. However, termination of pregnancy is an option exercised by others.

In pregnancy, immune function is suppressed in both HIV infected and uninfected women with a decrease in immunoglobulin and complement levels noted in early stages and a more significant decrease in cell-mediated immunity later in pregnancy. These normal changes during pregnancy have led to concerns that the effect of pregnancy in HIV disease could lead to accelerating the progression of the infection.

The newly diagnosed woman needs to be reassured that the impact of pregnancy on HIV disease progression is negligible (WITS data) in the era of HAART. No significant differences in death, AIDS-defining illness or fall in CD4 count have been observed between cases and controls,[26] though studies show that HIV infected women with pregnancy are significantly more likely to develop bacterial pneumonia than their never pregnant controls. However, some studies suggest pregnancy as a positive factor in achieving maternal health gain.[27]

The possibility of pregnancy doubling the risk of transmission to a male partner has been recently suggested. In this study, the incidence of transmission from women to men was 1.6 outside of pregnancy and 3.5 during pregnancy and this remained statistically significant after adjusting for age, unprotected sex and contraceptive use.[28] Thus, pregnant female-to-male transmission needs greater attention as biological changes that occur during pregnancy may make women more infectious than they otherwise would be.

Recommendation: Postexposure prophylaxis (PEPSE) and safe sexual practices including condom use in pregnancy should be encouraged in serodiscordant couples, while seroconcordant couples are made aware of the possible risk of superinfection.

Effect of HIV on CD4 and HIV RNA Levels in Pregnancy

The hemodilutional effect of pregnancy is associated with a decline in the absolute CD4 cell counts. For monitoring purposes in the pregnant state, the percentage of CD4 cells remains stable and will provide more accurate measurements. When comparing changes in CD4 count over time, no differences between pregnant positive women and nonpregnant women have been observed.[29] Similarly, in the absence of treatment, the viral RNA levels remain stable throughout pregnancy, though a recent study demonstrated a positive effect of progesterone on HIV infectability and synthesis.[30]

Effect of HIV on the Course and Outcome of Pregnancy

It is often difficult to determine the relative contribution of HIV infection, drug use and inadequate antenatal care to adverse outcomes in these women.[31] As the reported

studies do not control for the presence of STIs like syphilis and other factors, HIV being a direct cause or a marker of a complex interaction of related medical and social conditions that affect pregnancy, is debatable.

Recommendation: Discuss interventions that will prevent mother to child transmission, include HAART, mode of delivery and avoiding breastfeeding.

Effect of Sexually Transmitted Infections (STIs) on HIV positive Pregnant Women

It is widely recognized that the sexual health of any HIV infected individual has practical implications. Despite a national STD control program being in operation in India since 1946, public health interventions for STI control still remain patchy. In addition, the public sector syphilis screening program implemented in 1950 for pregnant women, lacks systematic application. This is further compromised by the fact that nationally only 57 percent of women in India receive antenatal care in the public sector with only a third (33.6%) of births attended by a healthcare professional and less than a quarter of births occurring in institutional settings.[32,33] Similarly, studies in India among men and women have found a high prevalence of reported "abnormal discharge," often with no defined cause for the genital symptoms and a poor correlation between self reported symptoms and laboratory confirmed infections.[34,35]

There is an urgent need to prevent these genital infections as surveillance data from BSS and National AIDS Control Organization (NACO, India) have reported that the incidence of HIV/AIDS is higher among those with pre-existing STIs.

It has also long been recognized that genital ulcerative diseases are associated with sexual transmission of HIV.[36] Coinfection with other STIs or the prevalence of genital lesions in either sexual partner amplify the risk of HIV acquisition or transmission.[37] The association between immune activation, mucosal inflammation, HSV and HIV-1 RNA genital tract shedding has been proven.[37,38,39] Several studies have confirmed this biological and epidemiological synergy, including a recent study from southern India[40] where an association between HIV and HSV-2 prevalence in antenatal clinics is reported.

Though the diagnosis and treatment of genital infections in a pregnant woman has benefits, currently there is no evidence to suggest that treatment has a direct impact in reducing MTCT. However, some observational studies suggest an association between infection, prolonged rupture of membranes, preterm labor and transmission.[41,42]

Rationale for a Genital Screen in Pregnancy

There is evidence that suggests infections with Chlamydia trachomatis, Neisseria gonorrheae, Ureaplasma urealyticum and Bacterial Vaginosis (BV) are associated with chorioamnionitis.[43,44] A recent study has shown a strong maternal HIV risk acquisition and premature delivery in women with BV.[45] It has also been shown that organisms causing BV stimulate HIV expression.[46,46a] In addition, treatment of Chlamydial and gonococcal cervicitis has been shown to reduce HIV-1 RNA mucosal shedding.[47]

A randomized, double blind, placebo controlled trial of herpes-suppressive therapy in HIV-1/HSV-2 infected women taking HAART in Burkina Faso, demonstrated that Valacyclovir 500 mg twice daily further reduced genital HIV replication in those women with residual HIV shedding suggesting an increased risk associated with HSV shedding while on HAART.[48] There is increasing evidence of compartmentalization of HIV-1 between the plasma and genital tract, with HIV RNA detected in the genital tract in the presence of an undetectable plasma viral load. There are also reports of genetic diversity of virus between the two compartments.[49,50]

These observations have clear clinical implications. As differential drug penetration in body compartments and the presence of genital tract infections are postulated amongst the causative factors of transmission, it would therefore seem reasonable to screen and treat pregnant women for STIs, especially as more women on HAART with undetectable plasma viral loads opt for vaginal delivery. Further, those booked for an elective cesarean section may develop premature rupture of membranes (PROM) with a subsequent vaginal delivery.

Syphilis in HIV Infected Pregnant Women

Pregnancy does not alter the clinical manifestations or serologic and treatment response for syphilis. Adverse pregnancy outcomes with prematurity, stillbirth and neonatal death (50%) are seen in untreated primary and secondary infection. Treatment of pregnant women should be based on penicillin regimens appropriate for the stage of syphilis.[51] Even with appropriate treatment, fetal infection may still occur and all neonates should be carefully evaluated to rule out congenital infection.

Genital Herpes Simplex Viral Infection (HSV) in Pregnancy

Congenital infection with HSV infection is uncommon. Maternal HSV shedding at delivery is associated with neonatal HSV infection, the risk being greatest when primary infection is acquired close to delivery (50%) with only 0 to 3 percent of neonates becoming infected in recurrent maternal disease. In order to avoid HSV acquisition during the pregnant state, women, especially if HSV seronegative, should be counseled regarding the avoidance of unprotected sex, particularly if the male partner has a previous history of oral/genital sores or serological evidence of HSV infection. Treatment with

antiviral drugs like acyclovir can be safely considered in pregnant women in the primary attack and late pregnancy and suppressive treatment for recurrent attacks. There is no evidence of an increased risk of birth defects or other adverse pregnancy outcomes with its use. There is no safety data currently available with Famciclovir and Valacyclovir use in pregnancy.

Human Papilloma Virus (HPV) and Cervical Dysplasia in Pregnancy

During pregnancy, genital warts often enlarge, are less responsive to treatment and usually resolve after delivery. This information should be provided to the patient and treatment with liquid nitrogen can safely be considered if patient insists on treatment. Podophyllotoxin should not be used in pregnancy as it is considered teratogenic. In women with suspicious, warty lesions (pigmented, bleed easily) unresponsive to treatment, biopsy can safely be considered to obtain a histological diagnosis, even during pregnancy.

HPV infection remains a major cause of dysplasia in this population with an increased prevalence of squamous intraepithelial lesions (SILs). Studies indicate a risk five times greater in HIV+ than in HIV negative pregnant women and recommend opportunistic cervical screening to be considered even in pregnancy, especially in females with CD4 counts <200 cells/mm^3 and especially in those women who have not had one in the recent past.

Little data exists on the prevalence of cervical dysplasia, or the percentage of women (and men) infected with human papilloma virus (HPV) in India. Though estimates vary, cervical cancer contributes significantly to the burden of morbidity and mortality in Indian women, with 90,000 new cervical cancer cases arising annually. The absence of a nationwide screening program means that many women may not present for care until the cancer is at an advanced stage (Institute of Cytology and Preventive Oncology, Indian Council for Medical Research). Though the Papanicolaou smear still remains the routine for women in a large part of the world, in places like Africa and India the feasibility of systematic smear screening in prenatal or gynecological clinics remains to be assessed.[52]

Colposcopic examination should be considered if dysplasia is detected on cervical screening in any woman. Cervical biopsy may be required if invasive disease is suspected in a pregnant woman, otherwise treatment can be deferred till after delivery. The role of HPV vaccine in HIV infected women or in pregnancy is yet to be clarified.

Recommendation: All HIV positive pregnant women should be screened at antenatal booking for genital infections (including STIs) and this is repeated at 28 weeks or predelivery. Infections when detected should be treated in accordance with the national guidelines.

AIDS Defining Illness in HIV Infected Pregnant Women

In general, the presentation and management of these women is similar to those in HIV infected women in a nonpregnant state.

Candidiasis in Pregnancy

HIV infected women may particularly be at risk of repeated symptomatic vulvovaginal infections. Only topical agents like azoles should be used for a minimum 7 day period. Systemic treatment with Fluconazole (100 mg dose × 7-10 days) in the first trimester has been associated with craniofacial and skeletal abnormalities;[53] however using a lower dose (<150 mg) so far has not shown any increased risk and may be considered after the first trimester in symptomatic females.

Esophageal candidiasis when symptomatic, may require treatment with liposomal amphotericin even in the early stages of pregnancy. No teratogenesis has been reported so far.

Pneumocystis Jirovecii Pneumonia (PCP)

Women diagnosed in late stages of HIV infection are at increased risk of PCP and this condition may have fatal consequences for both the mother and the unborn child.

The treatment of choice is Trimethoprim Sulfamethoxazole. However, concern remains regarding its use in the first trimester with increased risks of neural tube defects, cardiac and renal malformations.[54] If necessary, consider use in exceptional situations only and supplement with folinic acid (5 mg) as this has shown to be protective. Also, one needs to remember that CD4 reduction may be a spurious effect that is pregnancy related, CD4 percentage being a better indicator of immunosuppression.

Alternative treatment that may be considered are Clindamycin (safe), Primaquine (hemolysis reported) and Dapsone with trimethoprim (limited data). Steroid use is indicated as is the standard in nonpregnant women.

Co-trimoxazole still remains the drug of choice in PCP prophylaxis and the alternatives that are available are once daily Dapsone, nebulized Pentamidine, Clindamycin, Primaquine or Atovaquone (though limited evidence is available for the latter three drugs).

Cytomegalovirus Infection

Most maternal CMV infections are asymptomatic and should be considered in pregnant women with a mono-

nucleosis like clinical presentation. There does not appear to be an increased CMV perinatal transmission risk in HIV pregnant women with similar infection rates reported in infants of HIV uninfected and infected CMV seropositive women. It is recommended that CMV serology should be taken as a baseline test in all pregnant women, especially with low CD4 count and though seropositivity is commonly observed, primary prophylaxis is not recommended.

To reduce risk of exposure, CMV antibody negative blood products should be considered, if required, during pregnancy. All the available drugs that are currently used in systemic disease like Ganciclovir, Valganciclovir, Foscarnet, Cidofovir have been associated with congenital anomalies in animal studies. If necessary, consider using intravenous Ganciclovir or oral Valganciclovir as these agents have been mainly used in clinical practice and some safety data is currently available.[55]

Mycobacterium Tuberculosis (TB)

Mycobacterial infection remains the most common opportunistic infection, especially seen in developing countries with a high incidence of TB. Possible factors that may contribute are: TB conversion rates of 5 to 10 percent every year in HIV infected individuals after infectious contact, smear positive rates between 21 to 83 percent and HIV infection leading to 20 fold reactivation risk of latent TB.[56,57] In addition, TB presenting as immune reconstitution inflammatory syndrome (IRIS) in pregnant women following the commencement of HAART to prevent MTCT, remains a concern. Further, pregnant women are at risk of developing symptomatic disease and TB remains an independent risk factor for maternal mortality besides other factors like low birth weight, preterm labor and intrauterine growth retardation.[58]

In pregnancy, potential delay or difficulty in performing necessary investigations should not lead to a delay in treatment and should be considered in suspected cases, to prevent neonatal transmission of TB.

Management of the infection in the pregnant state is similar as for the nonpregnant female, using the well established four drug regimen of Isoniazid, Ethambutol, Pyrizanimide and Rifampicin. Although these drugs have been extensively used in pregnancy and have a good safety profile, in HIV co-infected pregnant women their use is complicated by the drug-drug interactions with HAART (especially seen in NNRTIs and Protease Inhibitors class of drugs). Rifampicin, Rifabutin and Azole antifungals also are metabolized via the cytochrome P450 enzyme system and will require some adjustments if co-administered with HAART. It is recommended that therapeutic drug monitoring (TDM) be used to guide treatment decisions with these agents in such situations.

Common interactions that may need to be considered are:

- Co-administration of Rifampicin will reduce the concentration of most ritonavir boosted PIs like Lopinavir, Saquinavir, Atazanavir and Darunavir, risking HIV viral control.
- Rifampicin use is also contraindicated with Saquinavir based PIs due to some severe cases of hepato-toxicity.
- Rifampicin can be used with Efavirenz (EFV) though the teratogenic effects of EFV may preclude its use especially in the first trimester of pregnancy. However, if the woman is already on EFV when pregnant, it may be prudent to continue with the drug, making dose adjustments according to maternal weight and therapeutic drug monitoring, if locally available.
- One may also consider using a triple nucleoside regimen in pregnant women who also require antituberculous treatment.
- In those HIV infected pregnant women with low viral loads (less than 10,000 copies/ml) and requiring anti-TB treatment one may consider Zidovudine monotherapy only, followed by an elective cesarean section, as antiretroviral prophylaxis is required to prevent MTCT only.

For more information on drug interactions you may consider using the following web based reference sources:

a. ***www.HIV druginteractions.org***
This is the Liverpool HIV drug information website that gets updated regularly as information and data keeps changing.
b. ***www.hivclinic.ca/main/drugs_interact.html***
This is the Toronto Clinic website that is also a useful resource.

Multidrug Resistant TB

Management of multidrug resistant TB (MDR-TB) is fraught with difficulties as there is limited experience of using second line drugs in pregnancy. However, there are reports of some of these cases being successfully managed in specialist units and the opinion of specialists in this field should be sought.[59]

Mycobacterium Avium Complex (MAC)

Management of infection in pregnancy is similar as in nonpregnant women; consider weekly Azithromycin/ Clarithromycin with CD4 counts less than 50 cells/mm^3. Use of macrolides in these cases has not been associated with an increased risk of malformations.[60]

Cryptococcus Neoformans (CN)

When diagnosed during pregnancy, CN will require treatment with Liposomal amphotericin. Flucytosine use in combination with Liposomal amphotericin has been

associated with teratogenic effects and should only be used when the benefits outweigh the risks. Consider Fluconazole as previously discussed, only in the later stages of pregnancy. There are no reports of Voriconozole use in pregnancy.

Toxoplasma Gondii

Routine baseline screening of all pregnant women for toxoplasma is recommended. Transmission to the fetus is known to occur only during active maternal infection though rare reports of transmission by reactivation of latent infection in HIV infection have also been reported.[61] Treatment with sulfadiazine/pyrimethamine may need to be considered; however, when used in the third trimester, methemoglobinemia and neonatal hemolysis remain a risk.

Folinic acid supplementation, preferably a higher dose (5 mg) is advisable in these cases. Other drugs that may be considered are Clindamycin/Pyrimethamine or Atavaquone.

Recommendation: Consider opportunistic infections in acutely ill pregnant women especially those with low CD4 counts, besides the possibility of Immune reconstitution inflammatory syndrome (IRIS) in those recently commenced on HAART. In pregnant women presenting with an AIDS defining illness and HIV negative previously, consider rapid HIV testing.

Associated Co-infections

Hepatitis B in HIV Infected Pregnant Women

Chronic HBV infection appears to have its natural progression modified by HIV co-infection. A significant increased mortality attributable to liver disease in co-infected patients, compared with those with HBV alone has been reported.[62] This has been attributed to decreased clearance rates of HBsAg and HBeAg, reactivation of HBV, higher levels of HBV-DNA and lower ALT levels, some of the important findings that differentiate HIV-HBV co-infected individuals from those infected with HBV alone.[63]

Vertical transmission (mother to infant) of infection by intrapartum contact with maternal blood and genital secretions can occur in 10 to 20 percent of pregnancies where the mother is HBsAg positive and HBeAg negative, with transmission rates increasing to 90 percent if the mother is also HBeAg positive. Most (>90%) of the infected infants become chronic carriers.[64]

Studies indicating maternal HBV DNA positivity is associated with a high rate of intrauterine transmission of HBV. In a program in India where 11,524 women were screened for HBV infection, maternal HBV DNA levels greater than 1.5×10^5 copies/ml were significantly associated with intrauterine transmission (P =.025), while mode of delivery and maternal HBeAg status showed no association.[65]

Controversies over the level below which HBV DNA concentrations are indicative of 'inactive' disease persist. Current HBV-DNA cut offs of 2×10^4, 2×10^3 and 2×10^3 IU/ml, are often used for HBeAg +ve chronic hepatitis, HBeAg –ve chronic hepatitis and cirrhosis respectively.[66]

Pregnant women with chronic hepatitis B should be referred to healthcare professionals with experience in the treatment of hepatitis B. The decision to treat takes into account other factors like pattern of disease, HBV DNA level, and presence or absence of significant necro inflammation and hepatic fibrosis.

Interferon use does not appear to adversely affect the embryo or the fetus.[67] However, this data is limited, and the potential benefits of interferon use during pregnancy should clearly outweigh the possible hazards. Lamivudine (3TC) has been used in HIV uninfected women with high HBV DNA viral load in the third trimester in an attempt to prevent perinatal transmission of hepatitis B virus infection with reports of mixed success rates.[67,68]

In HIV/Hep B co-infected females, Lamivudine (3TC) or Emtricitabine (FTC) should only be used in combination with Tenofovir, because of the rapid high rates of resistance that occur when 3TC/FTC are prescribed as the only HBV-active agent.[69,70] These drugs should be used as first line agents when tailoring antiretroviral therapy regimen in these patients. Achieving suppression of hepatitis B and HIV viral replication will lead to a delay in liver damage besides preventing MTCT.

All infants born to HBsAg positive mothers should receive hepatitis B vaccine, usually in combination with Hepatitis B specific Immunoglobulin (HBsIg) 200 iu intramuscularly at birth, one month, and six months of age.[71] This will reduce vertical transmission by approximately ninety percent. If HBsIg is not available, vaccination alone will prevent vertical transmission in 66 to 100 percent. Infants should be tested for hepatitis B (HBsAg and anti-HBs) 4 to 6 weeks after the last dose of vaccine.

There is no evidence to suggest that breastfeeding increases the risk of transmission. Arrangements should be made for Hep B screening and if required Hep B vaccination of children, household and sexual contacts if non immune.

Hepatitis C in HIV Infected Pregnant Women

Low rates of vertical transmission (5% or less) have been observed in HCV RNA positive women.[72] Higher transmission rates (up to 40%) have been reported in HIV co-infected women associated with detectable high levels of serum HCV RNA levels.[73]

There is at present no clear knowledge about how best to reduce the risk of vertical transmission and as the mechanism of transmission (being either transplacental, during delivery or both) is not understood, therefore, minimizing blood exposure from the mother to the child is expected to be beneficial.[74,75] A small retrospective study has suggested cesarean section may reduce the transmission risk.[76]

While there is no evidence of additional risk of transmission with breastfeeding, women should be informed of the potential risk of transmission in pregnancy and this may warrant the avoidance of breastfeeding when possible, especially in women who harbor a high HCV viral load. Testing of an infant maybe undertaken after 1 year of age to allow the maternally acquired antibody to clear with some suggestions that some infants may clear the Hep C virus as well without any intervention.[77]

Hepatitis A and B vaccine should be offered to all women with Hepatitis C infection.

Immunization in Pregnancy

Hepatitis B, pneumococcal and influenza vaccines are recommended for all HIV infected individuals and in unvaccinated women, these can be safely considered in pregnancy.

MMR and Varicella zoster are live vaccines and in susceptible women (IgG negative on antenatal screening) immunization should be delayed till after delivery.

Recommendation: All HIV positive pregnant women should be routinely screened for Hepatitis A,B and C.

Recommendations for the Use of Anti-retroviral Drugs in Pregnancy

***Scenario*: Known HIV positive woman not on HAART is now pregnant.**

Ideally all women who desire pregnancy should have had preconceptual counseling to optimize their health status prior to pregnancy.

Evaluation is indicated with regard to women requiring therapy for their own health.

If the pregnant woman meets the standard criteria for starting treatment as per the adult treatment guidelines and she presents in the 1st trimester, treatment should be started immediately and continued postpartum, taking care to avoid teratogenic agents like Efavirenz or DDI. HAART regimens have now been established as the standard of care for all HIV positive individuals requiring antiretroviral therapy (ARV).

If the pregnant woman does not require treatment for her own health and the primary reason to start treatment is to prevent MTCT only, then treatment can be delayed until after the 1st trimester (10 to 12 weeks) starting HAART between 20 to 28 weeks. Frequently in these cases the women stop treatment soon after delivery but other factors like adherence, nadir CD4 counts, patient preference, etc. may be taken into consideration and will guide this decision.

For those pregnant women not requiring treatment and reluctant to take HAART—zidovudine monotherapy between 20 to 28 weeks combined with intravenous zidovudine at delivery and stopping treatment post-delivery can be recommended.

***Scenario:* Known HIV positive women on HAART is now pregnant.**

The woman is advised to continue her antiretroviral treatment during pregnancy and postpartum especially if the regimen has been effective in causing viral suppression; use of Efavirenz or DDI is not recommended. However, most clinicians will continue patients on these drugs rather than switch treatment, especially if the patient's drug adherence is suspect or she presents later in the 1st trimester, as neural tube closure is almost embryologically complete by Day 26. It is also encouraging to note that prospective human reports so far in such cases to the Antiviral Pregnancy Register have not shown any increased toxicity or a cause for concern.

Recommendation: All pregnant HIV positive women should be advised to take HAART.

Medical Complications in HIV Positive Pregnant Women

Some medical complications may play an important role and increase the risk of mother-to-child transmission in HIV positive pregnant women. Hence, recognition and management of these conditions is an important element of antenatal care.

Nausea and Vomiting

As nausea and vomiting are common in early pregnancy, when starting HAART always consider the use of anti-emetic and antidiarrheal support, especially in the first trimester. The commonly used antiemetic drugs are Promethazine and Cyclizine; No teratogenic risk or interaction of these with antiretrovirals has been reported.[78]

In women presenting with intractable vomiting, while symptoms may suggest hyperemesis gravidarum (leading to fluid and electrolyte disturbances and nutritional deficiency) and requiring implementation of supportive treatment, consideration of conditions like lactic acidosis, pancreatitis and hepatitis presenting with these symptoms will be necessary in these patients. Temporary cessation of ARV treatment may also become necessary in some of these cases.

Bleeding in Pregnancy

Vaginal bleeding due to placenta previa and placental abruption may occur in early pregnancy. The management of such HIV infected pregnant women should be similar to uninfected pregnant women. However, the increased risk of mother-to-child transmission, besides the risks to the fetus of continued blood loss and prematurity will need to be considered.

Thromboembolism

Thromboembolism remains a considerable concern in pregnant HIV positive women. Besides pregnancy being a hypercoagulable state in itself, HIV infection also per se maybe associated with acquired thrombophilia and consequent complications like *in utero* fetal death, pre-eclampsia and intrauterine growth retardation. Other factors that increase the risk of thromboembolism include coexisting nephropathy (especially IgA nepropathy) and proteinuria associated with HIV infection with risks of hypertension and PET.[79] Consider antithromboembolic prophylaxis if a HIV positive pregnant woman requires hospitalization for whatever reason.

Malaria in Pregnancy

Malaria in pregnancy can lead to high maternal and infant morbidity and mortality and has been associated with increased risk of mother-to-child transmission of HIV.[80] Current recommendations are that intermittent treatment with an effective, preferably one-dose, antimalarial drug should be made available to all such women in highly endemic areas. This should be started from the second trimester and given at intervals of not more than one month apart.

Gestational Diabetes

Maternal use of drugs like PIs with their associated metabolic complications of glucose intolerance, dyslipidemia, type 2 diabetes mellitus remain an ongoing concern and cohort studies investigating this association have so far yielded conflicting results.[81,82]

Abnormal Liver Function Tests

These are increasingly being reported in HIV positive pregnancies.

In addition to pregnancy related conditions like pre-eclampsia, obstetric cholestasis, HELLP (Hemolysis, elevated liver enzymes and low platelets) syndrome and acute fatty liver of pregnancy, causing transaminase abnormalities, conditions like hepatitis, pancreatitis and lactic acidosis need to be excluded. Unconjugated hyperbilirubuneimia (Atazanavir related side effect) is also well recognized. Hepatic abnormalities occurring as a drug related (PI) effect have also been reported in pregnant women.[83]

Lactic Acidosis

This condition is rarely encountered in developed countries as it was usually seen in women taking DDI or d4T. The presenting symptoms are nonspecific in most cases, manifesting with elevated hepatic transaminases, gastrointestinal disturbances, fatigue, low grade fever and occasionally breathlessness. Monitoring lactic acid levels (2 to 4.9 mmol/l) is necessary as treatment interruption will have to be considered (45 mmol), if required. A high index of suspicion is required as is a need for close monitoring of women on these drug regimens, as the condition can be fatal.

Recommendation: While the medical complications in pregnancy need to be managed as in HIV negative women, the adverse effects of HAART need to be considered in these women highlighting the need for close liaison between the obstetric and the HIV team.

Fetal Malformations

At present no evidence of increased risk has been observed. The Antiretroviral Pregnancy Registry (www.apregistry.com) collects observational information on antiretroviral exposure during pregnancy to assess anomalies after HAART exposure. Current reports indicate that except for DDI (causing increased congenital malformations when exposed *in utero*) and Efavirenz (causing neural tube defects in animals), none of the antiretrovirals have given any cause for concern. There remain a growing number of multidrug class experienced females that are being exposed to newer classes of drugs in pregnancy and ongoing vigilance will be required. This also highlights the need for preconceptual counseling and support for those HIV infected women in their reproductive years and discussion about plans for starting a family. The possibility remains that at present many pregnant HIV positive women will be potentially exposed to teratogenic drugs or newer classes of drugs.

Recommendation: Current observations indicate that offering dating and anomaly scans as per national guidelines may be adequate.

Obstetric Complications in HIV Positive Pregnant Women

Spontaneous abortion

Limited data is available though earlier studies have suggested that HIV infection increased the risk of first trimester pregnancy loss like miscarriage and ectopic pregnancy, but this is yet to be confirmed.[84]

Stillbirth

Increased risks have been noted only in the developing countries.

Perinatal mortality

No evidence of increased risk has been reported in the developed countries.

Infant mortality

Limited data is currently available in the developed world.

Intrauterine growth retardation

Possibility of increased risk has been reported and needs assessing.

Low birth weight (<2500 gm)

Though previous reports indicated an increased risk, there is encouraging evidence that this has declined among infants during the HAART era. However, on comparing with the general population (US), higher rates are still seen in HIV infected women though non HIV related factors may be a contributory cause, i.e. maternal drug and alcohol abuse, etc., (Pediatric Spectrum Disease, PSD study).

Pre-eclampsia

While some studies have shown an increased risk with HAART, a recent study has shown no increased risk when compared to uninfected controls (0.8% vs 10.6%).[85]

Oligohydramnios

Very limited data is currently available.

Chorioamnionitis

Earlier studies have reported increased histological placental inflammation, especially in women with preterm deliveries. Several studies on HIV in Africa conclude that chorioamnionitis remains a risk factor for perinatal HIV transmission and infant mortality.[86] It is still unclear if it is a responsible factor for *in utero* transmission.[87]

Preterm delivery

Current guidelines recommend NRTI and PI based therapy as first line treatment during pregnancy. Some cohort studies from Europe, UK and Ireland consistently report an increased risk of preterm delivery, especially in women on Protease Inhibitor (PI) containing HAART regimens (14.1%) than in those on mono/dual treatment.[88] A recent meta-analysis has also revealed a trend towards increased prematurity with PI regimens (OR1.24) but was not statistically significant.[89] This association is more marked in premature births of less than 32 weeks gestation. This observation, however, is not reported by other groups, the increased risk currently remaining unexplained.

Preterm Prelabor Rupture of Membranes in HIV Positive Women (PPROM)

PPROM is associated with 40 percent of preterm deliveries and can result in significant neonatal morbidity and mortality in the general population. In the absence of chorioamnionitis, in most cases management is usually expectant and delivery is considered at 34 weeks with a small risk of preterm delivery and neonatal morbidity and mortality.

Most of the current recommendations are based on good clinical practice as there is no evidence base to guide decision making. All the existing data on risks of HIV transmission are from the pre-HAART era when prolonged rupture of membranes and chorioamnionitis was associated with an increased risk of mother-to-child transmission.[90] A meta-analysis of studies conducted before HAART use in pregnancy has demonstrated a 2 percent incremental increase in transmission risk for every hour of ruptured membranes up to 24 hours.[91] A recent Spanish study conducted in 500 HIV positive women has found that rupture of membranes for greater than 6 hours was associated with a three-fold increase in transmission risk in women not on HAART with no increased risk observed in women on HAART.[92]

The management of threatened cases of premature rupture is no different from that of HIV negative pregnant women, with women at presentation offered a vaginal swab for bacteriology and two doses of intramuscular Betamethasone (12 mg) 24 hours apart to encourage fetal pulmonary maturation.[93]

Where PPROM occurs before 34 weeks: Always consider the option of prolonging the pregnancy taking into account factors like the mother's virological status and level of viremia, presence or absence of maternal HAART and pregnancy or HIV related comorbidities. As discussed earlier, starting steroids immediately, excluding genital infections, commencing Erythromycin and having a low threshold for intravenous broad-spectrum antibiotic use, like Cephalosporins and Metronidazole will be necessary.

Attempt should be made to optimize the woman's HAART regimen to reduce the risk of mother-to-child transmission. Maternal single dose Nevirapine (NVP) should be strongly considered, even in scenarios where the possibility of the presence of NVP associated resistance exists. Nevirapine, if given 2 hours before delivery achieves highly effective transplacental transfer levels and the ability to provide prolonged drug plasma

concentrations lasting up to 7 days in a neonate that may be unable to have oral medication. Maternal HAART must be continued regardless of your plan, if the woman has detectable plasma viremia at presentation. Consider intravenous Zidovudine as well.

Delivery may have to be expedited if there is evidence of chorioamnionitis or fetal distress. However, further management should be guided by an assessment of the risks associated with prematurity, HIV transmission, availability of neonatal facilities and maternal health.

Where PPROM occurs after 34 weeks: Regardless of maternal viral load and therapy consider delivery of the baby after ensuring fetal lung maturity has been achieved as detailed in the management plan above.

Where PROM occurs at term: Management is determined by the pre-delivery plan for the patient. If a vaginal delivery is planned and undetectable maternal viremia has been achieved, administer broad spectrum antibiotics to cover for chorioamnionitis and expedite delivery with induction of labor (nb compartmentalization between genital tract /plasma)[94] to avoid the possible increased risk of transmission with prolonged rupture of membranes.

If a cesarean section is planned and detectable maternal HIV virus or other pregnancy related issues occur, early delivery by cesarean section is recommended. In some cases, in spite of a planned cesarean Section, vaginal delivery may become imminent, so consider NVP loading and antibiotics as described above.

Recommendation: All pregnant women should be advised about the increased risks of preterm delivery (one and half times) possibly HAART related. If a woman presents late in pregnancy or in labor and is diagnosed with HIV infection administer HAART as soon as possible and consider delivery by cesarean section.

Prolonged Pregnancy

The management of prolonged pregnancy in HIV positive women and the decision regarding induction has to be individualized to each patient and is difficult. The association of artificial rupture of membranes (ARM) with increased risk of MTCT remains, particularly if the maternal plasma viral load is detectable and the consequent trauma to the fetal scalp increases the risk of exposure to maternal blood and cervicovaginal secretions. However, there are no contraindications for induction with membrane sweep or use of prostaglandins.

Scar dehiscence and risks of transmission in HIV positive women leading to increased transmission is currently unknown. A trial of scar may be justified in a woman with a previous cesarean section who is currently on HAART, has an undetectable virus and spontaneously goes into labor.

Management of Delivery

The team should discuss details of the mode of delivery with the patient between 34 to 36 weeks and document the plans. This will be determined by the predelivery viral loads as vaginal delivery will be offered to women on HAART with undetectable levels. HAART should be continued during labor, avoiding invasive procedures like fetal blood sampling, etc. If instrumentation is needed, forceps use rather than ventouse is advisable to facilitate delivery.

If elective cesarean section is planned it is performed at 38 weeks; intravenous Zidovidine is started 4 hrs before the procedure and continued till the umbilical cord is clamped. In women with an undetectable viral load and requiring an urgent cesarean section, delaying surgey to administer the Zidovidine infusion is not necessary.

Delivery by cesarean section is also to be considered in women with a detectable viral load, Zidovidine monotherapy, co-infection with Hep C infection. Suggested operative management of these cases is to maintain a hemostatic field, avoiding rupture of the membranes till the fetal head has been delivered and early clamping of the cord postdelivery. Previous studies showing higher postpartum complication rates in these women have not been substantiated and antibiotic use should be considered as per the national guidelines.

Recommendation: A management plan for delivery should be documented between 34 to 36 weeks for all pregnant HIV positive women.

Postpartum Care

The postpartum care of HIV positive women is similar to that for uninfected patients though they may be at increased risk of postpartum complications like wound infections, etc.

Breastfeeding has been shown to double the risk of MTCT and all HIV positive women in developed countries are encouraged to avoid breastfeeding. This aspect of care needs to be discussed early in pregnancy to identify if the woman has any reservations and if so support needs to be provided. If suppression of breast milk is required, Cabergoline 1 mg stat oral dose within 24 hours of birth will need to be given.

Mother who chooses to breastfeed should be advised of the transmission risks associated with cracked nipples, mastitis or of oral lesions in the child. Reduced duration of breastfeeding and early weaning may be encouraged to reduce the risk of transmission. The maternal plan of care should ensure the follow-up for her child including HIV testing.

Recommendation: All HIV positive women should be advised to avoid breastfeeding.

Management of the Neonate

Detailed management will be discussed in another chapter; however, some guiding principles are as follows:

All neonates are given postexposure prophylaxis with antiretrovirals for a 4 to 6 week period starting at birth. If the maternal treatment regimen does not have Zidovidine, an alternative monotherapy can be given to the infant.

Infants of untreated mothers and those mothers with detectable viremia at delivery are given HAART as prophylaxis.

All neonates are tested for HIV at birth, 6 weeks and 3 months of age.

The standard test to detect neonatal infection is the HIV DNA PCR on the peripheral blood lymphocytes as it will take about 18 months for the maternal HIV antibody to disappear from the infant's plasma and performing HIV antibody testing during this period is not advised in the neonate. HIV antibody testing may be done at 18 months in the baby as a confirmatory test only. It is also suggested that a positive HIV DNA PCR before 1 week of age in the infant is indicative of possible intrauterine HIV transmission. Increasingly HIV RNA is also being used for testing purposes. Cotrimoxazole should be given as prophylaxis for all infants born to women with severe immune suppression and high risks of transmission.

Contraception Advice

During pregnancy: Pregnancy increasing the risk of HIV transmission in discordant couples has been discussed.

After delivery: This is often a neglected area and advice needs to be provided at the first post-natal visit. If the woman remains on HAART after delivery, review of her treatment regimen and the hormonal preparations that maybe considered for contraception and whether they can be safely coadministered without interactions is necessary.

Guidance on the interactions can be sought on http://www.bhiva.org/UKGuidelines2008.aspx

Plan of Care

The antenatal care of a HIV infected pregnant woman needs to be managed by a multidisciplinary team (MDT) which may comprise of HIV specialists, obstetricians, pediatricians, midwife and social service providers. The composition of this team will vary depending on the setting. Protocols should ensure there is designated responsibility for follow up and further care. It is imperative that the team involved in the patient's care are aware of her diagnosis and they plan in real time as the management of these cases may continuously alter. The patient should be made aware of the interventions with due explanations provided.

Recommendation: All HIV positive pregnant women should be managed by a multidisciplinary team that should at least include the following: HIV physician, obstetrician, pediatrician and specialist midwife—See Appendix to chapter 3.1, given after this chapter.

Antenatal Evaluation and Monitoring Principles

History of previous STIs, genital infections, vaccination is sought in addition to the routine pregnancy related booking details.

HIV history: Date of diagnosis, previous exposure to antiretroviral drugs, CD4 history, HIV related symptoms, infections, malignancies, family history of heritable diseases is elicited.

Baseline tests evaluating maternal health, blood count, renal and liver function tests are routine and are regularly repeated especially on commencement of HAART to check for drug toxicity. HLA B 5701 testing to detect women predisposed to Abacavir hypersensitivity should be considered.

Blood count is useful to evaluate anemia in women taking zidovudine. Serum bicarbonate is a useful marker in women on DDI or d4T to exclude lactic acidosis.

Additional blood tests should include Syphilis, hepatitis B,C, varicella zoster, rubella, measles, CMV IgG and toxoplasma IgG serology.

All pregnant women on antiretroviral treatment should be screened for gestational diabetes. Women should receive glucose screening with a standard, 1 hour, 50 gm glucose loading test at 24 to 28 weeks. Earlier testing may be considered in obese women, in advanced maternal age, those on PI therapy and a family history of diabetes.

Ideally in pregnant seropositive women, HIV assessment should include CD4 cell counts repeated every 3 months, HIV RNA plasma load taken every trimester, at 36 week gestation, and at delivery.

Genotypic Resistance testing is recommended where available in all pregnant women with a detectable viral load or showing suboptimal viral suppression before therapy is considered, as treatment adjustments may need to be considered. It should be noted that for this assay to be performed, the plasma viral load has to be >1000 copies.

Ultrasound is safe in pregnancy and routine screening for aneuploidy in the 1st trimester, dating and anomaly

scans is recommended and offered as per the national guidelines. Some clinicians offer a detailed fetal anomaly scan at 18 to 20 weeks gestation to women who have received ARV in the first trimester.

Radiography: It may be required when opportunistic infections are suspected. For any imaging undertaken, the consideration of potential harm should be balanced against the advantages of the investigation.

Chest X-ray using an abdominal shield may be undertaken but an abdominal X-ray or CT scan, should be avoided, if possible.

CT scan and using contrast to scan organs distant from the abdomen can be considered as well as MRI scan, though its use in the first trimester should be limited.

Gadolinium use in MRI scanning is contraindicated as it is has been found to be teratogenic in animals. Increasingly Ventilation/Perfusion VQ scan and CT pulmonary angiography use is becoming acceptable in cases of suspected pulmonary embolism in pregnancy as if untreated, this condition is associated with high maternal mortality rates.

Other procedures like biopsies, endoscopic procedures, lumbar puncture, etc. can be undertaken.

Sexual Health screening for genital infections is recommended at booking and repeated at 28 weeks as some observational studies have shown an association between genital infections, preterm labor and risks of transmission.

Invasive testing and Amniocentesis for genetic testing has been associated with a 2-4 fold increased transmission risk in the pre HAART era, though recent studies have failed to confirm this finding.[95]

In view of conflicting evidence, the following consensus has emerged that may be considered:

- All HIV positive women prior to invasive testing should be screened for Hep B, Hep C
- Try and achieve an undetectable maternal viral load with HAART and consider delaying the procedure, if possible, until this is achieved
- Consider commencing maternal HAART to provide cover during the procedure if the woman is drug naive. Consider using a drug or adding one that crosses the placenta like Nevirapine (NNRTI).
- Avoid inserting the needle through the placental route at all costs during the procedure.

Pharmacokinetics and Therapeutic Drug Monitoring (TDM) of Antiretrovirals in Pregnant Women

Pregnancy causes a physiologic background change that may lead to significant changes in the maternal pharmacokinetics. The various mechanisms that have been described are:

Absorption factors: Increased progesterone levels during pregnancy reducing gastric emptying and small intestine motility besides the impaired absorption caused by a raised gastric pH and nausea associated with pregnancy.

Distribution factors: The elevated body fat and water during pregnancy increasing the volume of distribution of both lipophilic and hydrophilic drugs. Plasma albumin and alpha acid glycoprotein concentrations decrease (hemodilution effect) also affecting protein binding.

Metabolic factors: Expression of cytochrome P-450(CYP) isoforms is affected during pregnancy, thus altering drug metabolism. Cytochrome induction is likely to be the main mechanism that explains the increased PI clearance seen in these cases.

Clearance factors: Increased renal blood flow during pregnancy may also increase the clearance of some drugs.

All these factors may lead to a significant variation of antiretroviral pharmacokinetics during the pregnant state.[96]

NRTIs

Drugs in this class like **Zidovudine** requires intracellular phosphorylation to become activated and hence plasma levels show a poor correlation for TDMs to be useful in clinical practice and are not recommended.

However, pregnancy does not seem to alter the pharmacokinetics of this class. For example, **Abacavir** exposure in a recent study has reported no modification was required, as with **Emtricitabine** (FTC) use, though the plasma concentrations in pregnancy may be decreased.

Similarly, **Tenofovir** (TDF) levels have been shown to be reduced in the last trimester of pregnancy compared to postpartum levels. However, the clinical significance of this finding has not yet been established.

It has also been noted that in pregnancy, the renal excretion of **Didinosine**(ddI) is increased, however this is not considered sufficient to necessitate dose adjustment in these women as very little data is available regarding its use. As in nonpregnant individuals, a reduction in the ddI dose is advised when Tenofovir is co-administered with ddI. However, recent European recommendations (2005) advise against the co-administration of these drugs especially in patients with a low CD4 count and high viral load (BMS letter Myers Squibb and Gilead, 2 March 2005) and should be avoided.

NRTIs have shown to penetrate the genital tract efficiently. Studies comparing genital tract levels with plasma show genital values as follows: Emtricitabine (FTC) 600 percent, **Lamivudine** (3TC) 300 percent, Tenofovir (TDF) 300 percent and Zidovudine (ZDV) 200 percent.[97] As yet the implications of these findings have not been ascertained in pregnancy.

NNRTIs

Class of drugs have a long half-life and are CYP 2B6 and 3A4 inducers.

When considering individual drugs for the pregnant women:

Efavirenz (EFV) there is no pharmacokinetic data on EFV in pregnant women as the use of EFV in pregnancy is not recommended.

Nevirapine (NVP) has been extensively used in both resource rich and poor settings especially as a single dose to prevent MTCT in the latter. While NVP is well-tolerated it has also led to an increase in drug resistance for both mothers and infants leading to high virological failure of NVP based regimens as evidenced when introduced 6 months later as part of their antiretroviral treatment.[98]

Studies assessing NVP pharmacokinetics have shown conflicting results.

PACTG 250 study when using 200 mg as single dose given prelabor showed a decreased concentration when compared to nonpregnant females (possibly due to increased clearance in pregnancy) while HIVNET 006 did not show any altered pharmacokinetics.

Similarly, PACTG 1022 study failed to show any pharmacokinetic difference between NVP when given 200 mg daily for 2 weeks, then increased to 200 mg twice daily.

A marked interindividual variability, with increased clearance in pregnant women may explain these results. However, in none of the studies, did they alter the clinical outcome with virological failure only seen in noncompliant individuals with no MTCT observed.

Though the predictive value of NVP plasma concentration has not still been established, a recent study has postulated the possibility of subinhibitory NVP plasma levels during pregnancy with subsequent viral resistance.[99]

TDM of plasma NVP levels is rarely clinically indicated.

Etravirine: There is no pharmacokinetic data regarding its use in pregnancy.

Protease Inhibitors

PIs are a highly protein-bound class of drugs with limited transplacental passage probably explaining why it is so well tolerated by infants.

Drugs that are currently in use are:

Nelfinavir (NFV): In nonpregnant adults, NFV has a highly variable bioavailability (80% with food) and elevated protein binding (>98%). The recommended Cmin is 1000 to 4000 ng/ml. It has been widely used during pregnancy and is well-tolerated but since 2007, its marketing and use has been questioned due to ethyl mesilate contamination and its associated risk of carcinogenicity.

Several studies have demonstrated a high variability in NFV pharmacokinetics and poor correlation with virological data. While this effect can be partly explained by small study populations, it has been well-established that by NFV clearance is increased during late pregnancy leading to a decrease in NFV exposure during the third trimester of gestation. Though the clinical impact of this observation is not known, a recent study raises the possibility of the risk of mutations with pregnancy, induced by NFV sub exposure. This observation may justify the use of TDM for dosage adjustment purposes in pregnant women.

Saquinavir (SQV): This is a lipophilic, high protein binding (approx 98%) PI. It is classified as FDA category B. The use of SQV hard gel, soft gel capsules or new formulation tablets when co prescribed with low dose ritonavir as a boosting agent is a safe and effective drug in pregnancy. All the available data suggests that SQV based regimens provide exposure above the target AUC>10,000 ng/ml-hr with no adjustments needed. However, as plasma concentrations are lowered in pregnancy with a high interindividual variability, TDM should be considered. Unboosted SQV (soft gel capsules) should be avoided in pregnant women especially in view of the low plasma concentrations that are achieved.

Lopinavir (LPV): This has been widely used and is the recommended PI during pregnancy with low dose Ritonavir. LPV/r capsules (133.3/33.3 mg) have recently been replaced by a tablet formulation which does not require refrigeration, is not influenced by food and demonstrates less interindividual variability. Similar results have also been demonstrated in pregnant women.[100] LPV is protein bound (98-99%) and is classified as FDA category B. Studies show that the postpartum, third trimester concentrations of Lopinavir (Lopinavir 400 mg/ritonavir100 mg) are reduced by 28 percent. The protein-free fraction is however moderately increased (17%) in pregnancy and at the standard dose prescribed little variation in individual plasma trough concentrations has been observed. Cohort studies have suggested that the majority of mothers taking the standard adult dose have adequate trough concentrations.

However, very little LPV is detected in the genital tract.

Atazanavir (ATZ): The absorption of ATZ is highly dependant on gastric pH, reduced bioavailability noted with acid suppressive therapy. In addition, gestation causing an increased gastric pH can be a concern.

ATZ like the other PIs is protein bound (86%) and is classified as FDA category B. Very little data exists regarding ATZ use in pregnancy. Some small studies have

demonstrated that at standard doses, boosted Atazanavir with low dose ritonavir has similar concentrations in the third trimester and postpartum.[101]

Indinavir (IDV): This PI is seldom used nowadays and very few studies have explored its use in pregnancy. It is the least protein bound PI (60%) and thus results in substantial penetration into the CSF with high concentration in the cervicovaginal and seminal secretions. IDV is classified as FDA category C. Results from small studies in women indicate that plasma concentrations remain variable, with low levels demonstrated in late pregnancy, these remaining unchanged following ritonavir boosting.

The pharmacokinetic data of other agents and newer drugs, like Tipranavir, Darunavir, Fosamprenavir and Maraviroc is not available.

To conclude, limited data is currently available regarding the PI formulations that are currently in use with protein binding effect demonstrated for Lopinavir only. In view of the considerable interpatient variability, therapeutic drug monitoring is recommended for PIs during pregnancy where facilities exist. Initial TDM monitoring should be conducted when steady state (2 weeks or more into therapy) has been achieved and may need repeating in the third trimester and is recommended in all PI based regimens.

Pharmacokinetic data shows that pregnancy significantly affects exposure to certain antiretrovirals particularly in the third trimester but the clinical consequence of this reduced exposure is still not clear.

Recommendation: Therapeutic Drug Monitoring (TDM) in some cases due to the altered drug pharmacokinetics, and drug-drug interactions seen during pregnancy.

Pharmacokinetics of Antiretroviral Drugs in Breast Milk

Transmission of HIV from mother to child after birth via breast milk remains a major problem in areas of the world where formula feeding is not safe, affordable or practical.

The extension of maternal highly active antiretroviral therapy (HAART) through the period of breastfeeding, has been proposed as a strategy to reduce breast milk HIV transmission by reducing plasma and breast milk HIV concentrations and/or by providing prophylaxis to the infant through ingestion of antiretrovirals, present in breast milk. Little is known about the safety of ARVs in breast milk, the benefits and risks to breastfed infants of exposure to maternal ARV drugs during lactation are also poorly understood.

Previous human studies have shown that antiretroviral drugs like Zidovidine, Lamivudine, Nevirapine administered during the last trimester of pregnancy and after delivery reach levels similar to or higher than plasma concentrations in breast milk and can significantly reduce HIV RNA levels, though the extent of antiretroviral transfer from mother to infant via breast milk and the resulting infant antiretroviral drug exposure have not been well delineated.

The different physicochemical properties of drugs lead to differential transfer from maternal plasma to breast milk and to the breastfed infant. Incomplete exposure of infants to some components of a maternal regimen may favor the selection of drug-resistant virus, should transmission occur. A study of ARV concentrations in exclusively breastfed Kenyan infants younger than 6 months, whose mothers were receiving HAART, achieved significant concentrations of the estimated median daily dose by breast milk, Nevirapine 600 μg/kg/d (15% of the 4 mg/kg/d infant dose being evaluated in PMTCT studies) and Lamivudine 182 μg/kg (2% daily treatment dose for>3-month-old) but not Zidovudine 1.35 μg/kg/d (<1,000 × lower than standard infant dose) for PMTCT. Lamivudine concentrations were just greater than the 50 percent inhibitory concentration (IC50) for wild-type HIV while the median Nevirapine concentrations (0.90 mg/l) were well above the median HIV IC50 (0.017 mg/l).[102]

Another study of Rwandan infants of mothers receiving an Efavirenz based HAART similarly achieved median Efavirenz concentrations of 0.87 mg/l through breast milk ingestion, just below the recommended target through concentration of >1 mg/l.[103]

These findings indicate transfer of NNRTIs from mothers receiving HAART may result in substantial exposure in their breastfed infants which along with the potential benefit of prevention of HIV transmission exposes the infant to the risk of side-effects besides the risk of developing viral resistance to NNRTIs should HIV transmission occur. Conversely, breast milk concentrations of PIs are low and there is little, if any, transfer to the infant via breast milk.[104]

Recommendation: TDM may play a role in optimizing individual dosing as drug concentrations in infants can be highly unpredictable, especially in neonates and premature infants, severely ill children or those treated concomitantly with other medications.

Appendix to Chapter 3.1

Perinatal Retrovirus Infection Care Plan

UNIVERSITY HOSPITALS OF LEICESTER NHS TRUST

Directorate of Women's and Perinatal Services

Patient Addressograph

☐ Leicester Royal Infirmary

☐ Leicester General Hospital

EDD ☐☐ / ☐☐ / ☐☐

SPECIALIST CARE TEAM

Specialists	Name	Contact Number	Date Notified
Community Midwife			
Specialist Midwives*			
GU / ID Physician			
GU Health Advisors			
Obstetrician			
Pediatric Team			
Pharmacist			

* The named midwives can usually be contacted between 0900 and 1700 hours Monday to Friday.

Date of diagnosis ☐☐ / ☐☐ / ☐☐

Timing of diagnosis ☐ Prior to pregnancy **or** Gestation at diagnosis ☐☐ wks

GP ☐ aware ☐ not aware

Birth partner ☐ aware ☐ not aware Name: ____________

Family ☐ aware ☐ not aware *(tick this if any members unaware)*

Responsibility of documenting details		Date	Signature	Print Name
This Page	Specialist Midwives			
Antepartum Plan	GU Medicine Team			
Intrapartum Plan	Obstetric Team			
Postpartum Plan	Specialist Midwives			

Perinatal Retrovirus Infection Care Plan

Antepartum Care Plan

Antenatal Discussions — Sign & Date

Vertical Transmission ☐ discussed ______
Antiretroviral Therapy (ART) ☐ discussed ______
Management of Labor/Mode of delivery ☐ discussed ______
Criteria for trial of vaginal birth ☐ discussed ______
Benefit of Cesarean section if above criteria not met ☐ discussed ______

Antenatal Checklist

Pediatric nurse consultation ☐ referred
Avoidance of breastfeeding ☐ discussed Sign ______ Date ______
Neonatal ART ☐ discussed Sign ______ Date ______
GU infection screens taken between ☐ booking ☐ 28 weeks Other: ☐ weeks
Other known infection noted ______
Resistance Bloods ☐ Yes ☐ No ______

BLOOD TESTS

Date	Gest (wks)	CD4	Viral Load	Hb	Platelets	WCC	U+E's / LFT's	Initials
Pre Del Bloods & Syphilis								

SWABS

Date	Gest (wks)	Chlamydia	BV	Gonorrhea	HSV	TB	Treatment Given

MEDICATION

Date	Gestation when started prepregnancy	Drug	Dosage	Frequency	Side Effects	Signature

Pediatric alert forms sent ☐ Yes ☐ Date ______ Signature ______
Maternal ART ☐ Continue ☐ Discontinue (postnatally)
Follow-up postnatally in GU/IDU ☐ Weeks

Perinatal Retrovirus Infection Care Plan

Intrapartum Care Plan

Mode of delivery – finalize plan at 35 - 36+ weeks Mother's Weight ☐☐☐ kg

☐ Elective cesarean section at 38/39 weeks Signature ____________

Planned Date ☐☐ /☐☐ /☐☐

Unless presents beforehand in advanced labor and vaginal delivery likely within four hours: then consider vaginal delivery using guidelines below: Date ________

Obstetric Pharmacist informed of delivery date Yes ________

Drug chart written in advance Yes ________

Admit mother to ward or Delivery Suite evening before delivery

Site iv cannula before midnight and commence AZT infusion at 07.00

Zidovudine (AZT) infusion to start 4 hours prior to cesarean section ☐ Not Required

(see IV drug folder for further information)

Zidovudine (AZT) 2 mg/kg IV over 60 minutes

Zidovudine (AZT) 1 mg/kg IV per hour

Do **not** discontinue any other antiretroviral medication

Senior obstetrician to undertake delivery

☐ Trial of vaginal delivery Signature ____________

Acceptable if viral load below lower limit of detection with ultrasensitive assay (<50 viral copies per ml), no active genital tract infection and low prior risk of intrapartum complications

☐ 28 week GU infection screen and predelivery virology results reviewed

Obstetric Pharmacist informed of plan ☐ Yes ☐ Not Required

Drug chart written in advance ☐ Yes ☐ Not Required

Await spontaneous labor unless obstetric indication to intervene

Active management of labor (two-hourly assessments)

Avoid ARM, use oxytocin with intact membranes, if necessary

Avoid FSE or FBS

☐ Intrapartum antiretroviral therapy **(see IV drug folder for further information)**

Zidovudine (AZT) 2 mg/kg IV over 60 minutes

Zidovudine (AZT) 1 mg/kg IV per hour throughout labor until the cord is clamped

Do **not** discontinue any other antiretroviral medication

- **Zidovudine injection is a stock item on delivery suite.**

☐ Prophylactic antibiotics to prevent chorioamnionitis (intrapartum use only)

Cefuroxime	1.5 g IV 8 hourly
Metronidazole	500 mg IV 8 hourly

If prelabor rupture of membranes

1. Be certain of diagnosis.
2. Induce / augment immediately using oxytocin.
3. Consider nonlabor cesarean section if low probability of delivery within 10 hours (i.e. primip with unfavorable cervical score or minimal progress after 6 hours augmentation).
4. **Neither cord blood nor placental pathology is routinely required in relation to retroviral disease.**
5. **Cord blood should not be taken for neonatal PCR testing.**
6. **Bath baby immediately on delivery suite.**

ERGOMETRINE should not routinely be given to women taking protease inhibitors (PIs), e.g. (not exhaustive list)–Kaletra, Fosamprenavir, Indinavir, Lopinavir, Nelfinavir, Ritonavir, Saquinavir.

PIs can increase the levels of ergot alkaloids. The interaction has only been noted with ergotamine but is considered to be a class effect. Ergotism (hallucinations, severe gastrointestinal upset, a type of dry gangrene caused by vasoconstriction and a painful burning sensation in the limbs and extremities) has been seen with just one dose of ergotamine.

Perinatal Retrovirus Infection Care Plan

Neonatal Care Plan

Baby's Name ______________________ Baby's Number ______________________

Date of birth ☐☐ /☐☐ /☐☐ Time of birth ☐☐ : ☐☐ Birth weight ☐☐☐☐ gm

Delivery ☐ elective cesarean section ☐ emergency cesarean section

☐ normal vaginal ☐ instrumental vaginal

Comments ____

Neonatal antiretroviral prophylaxis – must start within 6 hours of birth

Drug	**Dose**	**Duration of therapy**
Zidovudine (AZT)	4 mg/kg BD *	Four weeks
Alternative Treatment		

* If 34 weeks gestation or less for reduced dose

First dose Dose given (AZT) ☐ ☐. ☐ mg Date ☐☐/☐☐/☐☐ Time ☐☐:☐☐

☐ ☐. ☐ mg

☐ ☐. ☐ mg

Neonatal blood test taken on day 1, must reach lab by 4.00 pm (Mon – Fri only). Cord blood ***must not*** be used for this test.

Maternal Blood test – 7ml EDTA sample (red top) to be taken at the same time as the neonatal blood test.

2 ml EDTA sample—sample must be in Virology Lab, LRI by 1600 hours

Notify Consultant Virologist, that sample being sent

Virology form–both maternal and neonatal samples to be sent on the same form. Indicate that both samples sent.

Test request Diagnostic retroviral PCR

Clinical details State which maternal retrovirus may have been vertically transmitted.

Prior to infant discharge

Notify Pediatric Team ☐ done (contact details on front page)

NBBCG vaccination of the infant should be delayed until the result of all PCR tests are known.

Perinatal Retrovirus Infection Care Plan

Maternal Postpartum Care Plan

Avoidance of breastfeeding discussed

Advice accepted ☐ Yes ☐ Declined

Further individual plans made with patient if declined *Signature* ____________ *Date* ________

____

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____

Postpartum care

Routine obstetric postnatal check can be with GP

Review if maternal ART to be continued postnatally ☐ Continue ☐ Discontinue

Family planning discussion on:

☐ Advantages of barrier methods ☐ Relative contraindication of IUCD

Home Visit arranged ☐ Yes ☐ No

Medical follow-up plans discussed

☐ GU Medicine ☐ ID – Clinic 5

Appointment given to patient ☐ Yes Date ____________

Health Advisors Informed ☐ Yes ☐ No

Any Other Comments ____

____

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Signature: ____________ Print Name: ____________

Date:

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3.2

Vertical Transmission of HIV: An Update

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Introduction

One of the greatest successes in AIDS research to date has by far been the discovery of successful interventions that interrupt the transmission of HIV from mother to child. It is however important to note that these successes have occurred largely in countries with great resources and the least burden of perinatal transmission of HIV. In the developing world wherein currently 95 percent of vertical transmission of HIV occurs, it is highly condemnable that still every minute an infected infant is said to be born in spite of the fact that vertical transmission is largely preventable, mainly because translating knowledge into practice is not always possible or feasible. This has led to continuous growing numbers of children with HIV, thereby making pediatric HIV a looming problem rapidly draining the already burdened health care system of these countries. It is the need of the hour to appropriately address the challenges to achieve 0 percent transmission of HIV from an infected mother to her child thereby giving a hope for an AIDS-free new generation worldwide.

Throughout this document, except in the last section which has been dedicated to HIV-2, HIV refers to HIV-1.

Magnitude of the Problem

Every minute a child is infected with HIV, and everyday about 1000 childrens die of AIDS which claims roughly half a million young lives every year.[1] An overwhelming majority of these children are born in resource limited countries as a result of mother-to-child transmission (MTCT) during pregnancy, childbirth or breastfeeding and are potentially preventable. Overall, 20 countries in sub-Saharan Africa and East, South and South-East Asia account for about 90 percent of the pregnant women needing antiretrovirals to prevent mother-to-child transmission.[2] This signifies the possibility of infected babies being born in enormous numbers in these areas, unless vigorous prevention strategies are implemented. In India, of the estimated 1.8 to 2.9 million people living with HIV, 39 percent are women with a national average antenatal prevalence being 0.48 percent.[3] Also, India is a country where breastfeeding is a norm and a large majority of infants continue to breastfeed till about 2 years of age, posing an enormous challenge of safe breastfeeding practices in the context of HIV.

Factors Affecting Transmission

Maternal factors, viral factors, obstetric factors, fetal factors, infant factors all affect transmission making it essentially multifactorial. Maternal factors are seroconversion during pregnancy, advanced stage of the disease with high viral load and low immunity, concomitant malnutrition/micronutrient deficiencies/ sexually transmitted diseases, no/suboptimal therapy; In the intranatal period, risk factors for increased transmission are mode of delivery, prolonged contact with maternal blood/cervicovaginal secretions, prolonged rupture of membranes, chorioamnionitis, invasive procedures like episiotomy/fetal scalp electrode/ instrumental delivery. Thin skin, susceptible mucous membranes, immature immune functions and low levels of maternal antibodies make prematurity a risk factor for increased transmission. In the postnatal period, risk factors are breastfeeding, feeding with cracked nipples/ mastitis, mixed feeding, new seroconversion of the mother, high viral load, low CD4 cell count. In the absence of any intervention, rates of MTCT of HIV-1 can vary from 15 to 30 percent in developed countries and increase to 30 to 45 percent in developing countries, the difference mainly attributable to infant feeding practices that comprise almost universally of breastfeeds for prolonged duration.[4]

Interventions to Decrease Mother-to-Child Transmission of HIV

Primary Prevention

Preventing HIV infection in the first place in the women of child-bearing age through awareness and imparting of knowledge to the adolescent girls about safe sexual practices, sexually transmitted infections in general with HIV in particular, family planning measures all go a long way in controlling the pediatric HIV epidemic.[5]

Antenatal Prevention

The greatest challenge in preventing perinatal HIV remains the need to scale up coverage to the large majority of HIV infected pregnant women who do not currently receive Prevention of Mother-to-Child Transmission (PMTCT) services. It is estimated that globally <15 percent pregnant women get tested for HIV and <12 percent of seropositive women have access to antiretroviral prophylaxis in many resource-poor settings, including the simplest single-dose regimens.[6] Currently in India, 8 percent of HIV infected pregnant women are said to be receiving antiretroviral to reduce the risk of MTCT.[3]

Wide antenatal coverage with universal screening of all pregnant women as early as possible is the key to a successful antenatal prevention program. Equally important is imparting knowledge to even HIV negative pregnant women to provide them with the necessary information and support to remain uninfected. The positive women should be thoroughly evaluated clinically for any opportunistic infections including asymptomatic genital tract infections and treated for the same, as well as immunologically to guide regarding their treatment needs in addition to their routine antenatal care.

Antiretroviral Therapy in Pregnancy

Antiretroviral drugs (ARV) reduce the viral replication and thus, help to reduce MTCT of HIV by lowering the plasma viral load and also act as postexposure prophylaxis in the newborns. In resource rich countries, highly active antiretroviral therapy (HAART) has reduced the vertical transmission rates to around 1 to 2 percent[7-9] but unfortunately HAART is not yet widely available in low and middle income countries, where various simpler and less costly antiretroviral regimens are being offered. For a detailed overview of PMTCT till 2005, kindly refer to the overview published in the special edition of IJMR on HIV/AIDS by the same authors.[10] Single-dose Nevirapine (SD-NVP) remains the corner stone of PMTCT services in many resource limited settings including India. No doubt SD-NVP has been demonstrated to be safe, feasible and cost effective in the prevention of mother-to-child transmission of HIV but several major causes for concern have arisen with more and more information coming up challenging the appropriateness of it is usage for PMTCT. On the other hand, given the challenges that are recognized in the implementation of even SD-NVP for PMTCT, it's exclusion as an option for PMTCT would further reduce the effectiveness of the existing PMTCT programs with a likelihood of resulting in an escalation of the already staggering number of HIV infected infants. However, the fact remains that implementing regimens that do not fully suppress HIV replication promotes the development of drug resistance with a risk of compromising the efficacy of future treatment options for the mother (as well as for the infant, should the infant become infected despite the preventive intervention). It is unfortunate that the drugs that are used so commonly for PMTCT are the drugs that could lose efficacy following the development of a single resistance mutation, such as NVP (with cross resistance to Efavirenz) and Lamivudine (3TC). Non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance can be detected within the first 6 months after SD-NVP in up to 25 to 50 percent with the use of standard genotyping[11] and in as many as 60 to 89 percent with the use of more sensitive techniques.[12,13] Currently available preliminary data indicate that SD-NVP is effective for PMTCT in repeat pregnancies as well[14-16] and that SD-NVP exposure does not compromise future treatment with an NNRTI-regimen as long as treatment is initiated at least 6 months after SD-NVP exposure.[17,18] However, the potential risk of re-emergence of the archived mutant strains on repeat exposure to the drug should be borne in mind. It is particularly concerning that subtype C is associated with higher rates of NVP resistance (69%) because most HIV infections in India and other resource limited countries are of subtype C.[19,20] Resistance to 3TC can develop rapidly even when combined with Zidovudine (ZDV), because a single mutation in the HIV genome can result in high level resistance to 3TC.[21,22] There is also concern that the use of ZDV monotherapy in pregnancy may lead to the emergence of drug-resistant virus as studies have demonstrated ZDV associated resistance mutations in these women.[23,24] The high genetic barrier to resistance of boosted protease inhibitors (PIs) and their short plasma half-life make them a more attractive option for short-term ART than NNRTIs.[7,25-27] Use of adjunctive antiretroviral drugs to reduce resistance to intrapartum use of NVP have been investigated and found to be effective: The treatment option preservation study (TOPS) has demonstrated that the administration of ZDV +3TC during labor, in addition to SD-NVP, followed by ZDV+3TC given for 4 to 7 days after delivery reduced the development of NVP resistance from 60 to 10 percent;[28] a single dose of tenofovir and emtricitabine, taken with

antepartum ZDV and intrapartum NVP has shown to reduce NNRTI resistance mutations at 2 weeks and 6 weeks after SD-NVP ingestion by half.[29] In the light of more and more reports emerging pertaining to development of resistance in the short, suboptimal viral suppressive courses of antiretrovirals, there is a major cause for concern, given that not all drugs for optimal therapeutic regimens are available easily in the resource limited settings, where these preventive regimens are largely being implemented. The current WHO Guidelines (Table 3.2.2), for PMTCT includes initiation of anti retroviral therapy (ART) for all HIV infected pregnant women with CD4 cell count <350 cells/ mm, irrespective of WHO clinical staging; and for all HIV infected pregnant women in WHO clinical stage 3 or 4, irrespective of CD4 cell count. The criteria for initiating ART for eligible pregnant women are the same as for nonpregnant women and stresses on the need to start ART irrespective of gestational age and continue ART throughout pregnancy, delivery and thereafter. The infants born to these mothers receiving ART for their own health, should receive daily NVP until 6 weeks of age if breastfed and daily ZDV or NVP from birth until 6 weeks of age if not breastfed. The recommendation for all HIV infected pregnant women who are not in need of ART for their own health, is to provide ARV prophylaxis from as early as 14 weeks gestation (second trimester) or as soon as possible when women present late in pregnancy, in labor or at delivery.[30] Although maternal HAART is clearly warranted in women who require therapy for their own health, the benefits and safety of HAART used solely for PMTCT over a long-term period, in healthy women with HIV infection have not yet been demonstrated. Furthermore, the effect of these drugs on mothers and their exposed infants with regards to potential toxic effects or drug resistance needs further evaluation.

Intranatal Prevention

As a policy any pregnant woman without a documented HIV status at the time of labor should be screened with rapid HIV testing unless she declines, so that preventive measures, although less effective than if used in conjunction with antenatal measures combined, could be implemented at this stage too. Women with a positive rapid antibody test should be presumed to be infected until standard HIV antibody confirmatory testing clarifies their status. Particular efforts are needed to ensure that they receive HIV related services, including clinical and immunological assessments to determine their eligibility for ART as part of postpartum follow-up services. Artificial rupture of membranes should be avoided since ruptured membranes of more than 4 hours doubles the risk of transmission and so also invasive procedures such as fetal scalp monitoring or blood sampling, episiotomies, instrumental deliveries. Elective lower segment cesarian section (ELSCS) before labor and before the rupture of membranes has been shown to be safe and effective, however the risks and benefits of ELSCS solely for prevention of MTCT must be carefully weighed against any increase of morbidity or mortality for either the woman or her infant, as well as increased costs and recovery time. In a prospective study conducted in the perinatal clinic of a university affiliated maternity hospital in Mumbai[31] which included a four-pronged intervention consisting of the use of a shorter course with a lower dose of ZDV (400 mg/day for the last 6 weeks of antenatal period) coupled with ELSCS before the rupture of membranes, oral ZDV powder to the infant for 6 weeks following delivery (due to unavailability of oral suspension at the time of the study) and complete omission of breast milk, a striking success in reduction of perinatal transmission was noted (Transmission rates of 5.8 percent as against 24 percent in those who had not received any form of perinatal intervention).[31,32] As shown by several studies[33, 34] and also by our own experience, a short-term ART for PMTCT would benefit equally well and allow spontaneous normal delivery, avoiding many unnecessary ELSCS, a procedure that still carries a significant risk in many low-income countries. ELSCS is recommended at 38 weeks gestation for women with unknown or HIV RNA levels >1,000 copies/ml near time of delivery as per the DHHS Guidelines[7] and for women with >50 copies/ml on combination ART as per the BHIVA Guidelines.[35]

All HIV infected women who have not received antepartum antiretroviral therapy should have intrapartum component of antiretrovirals as they could be immensely useful as most transmission occurs near to or during labor and delivery: ZDV (Intravenous if available or per oral)/single dose NVP/ZDV + 3TC; The meta-analysis of individual records of data from African MTCT prevention trials indicated that a combination of ZDV and 3TC started during labor has similar efficacy to SD-NVP in preventing MTCT.[36] The WHO recommended ARV regimen for preventing MTCT among women in labor who have not received antenatal ARV prophylaxis consists of SD-NVP+AZT and 3TC intrapartum, and a seven-day tail of AZT+3TC for the mother, and for the infant SD-NVP and AZT for 4 weeks.[37]

As most HIV infections in children occur during the time of delivery and as both free and cell bound viruses have been found in cervical and vaginal secretions, theoretically, cleansing the vagina with an antiseptic or viricidal agent such as chlorhexidine could reduce this mode of transmission. There is scarcity of evidence to conclusively say that inexpensive modalities like cleaning/ disinfection of the birth canal can reduce MTCT although the incidence of neonatal sepsis is definitely cut down by these strategies.

Postnatal Prevention

Worldwide breastfeeding is a major significant route of MTCT where safe feeding alternatives are not easily available. Breastfeeding is normally the best way to feed infants with its benefits going far beyond sound nutrition; unfortunately both cell-associated and cell free HIV virus have been detected in breast milk. Late postnatal transmission through breastfeeding can account for up to 40 percent of the overall MTCT rates.[38-40] It has been suggested that breastfeeding transmission risk is higher during early lactation because of increased breast milk viral load in colostrum. The risk, however, continues throughout breastfeeding and is associated with low maternal CD4 count, duration of feeding, maternal viral load, mastitis, and mixed feeding. Seroconversion during lactation, advanced stage of the disease in the mother, concomitant vitamin A deficiency, breast conditions like cracked nipples and mastitis, have shown to increase the risk of postnatal transmission of HIV through breastfeeds.[41] Infant feeding practices in the developing world that comprises almost universally of prolonged duration of breastfeeds contribute to the higher rates of MTCT. Women with HIV infection should be fully informed of both the risks and benefits of breastfeeding and be supported in their decision about feeding practices. The overall objective is to prevent HIV transmission through breastfeeding while continuing to protect, promote and support breastfeeding for HIV negative women and in those of unknown status. When children born to women living with HIV can be ensured uninterrupted access to nutritionally adequate breast milk substitutes that are safely prepared and fed to them, they are at less risk of illness and death if they are not breastfed. However, when these conditions are not fulfilled, in particular in an environment where infectious diseases and malnutrition are the primary causes of death during infancy, artificial feeding substantially increases the risk of illness and death. Knowledge and commitment on the part of caregivers and a good level of ongoing support from counselors and/or social workers, safe water, assured supplies of affordable fuel, easy access to quality health care for mothers (including family planning) and infants are crucially needed for women choosing not to breastfeed.

Many antiretroviral drugs like ZDV, 3TC and NVP have all been detected in the breast milk of HIV infected women, which could probably lower the viral load in breast milk and be associated with a reduced risk of HIV transmission. However, the possibility of only some drugs penetrating the breast milk and/or in suboptimal concentrations that may not be sufficient to decrease viral replication promoting the development of drug resistant virus in the milk, which could be transmitted to the infant, should be borne in mind. Moreover, the toxicity of chronic ARV exposure of infants via breast milk is unknown. In resource-constrained environments, how best to continue to promote breastfeeding which is an important intervention for child survival, without exposing more infants to the risk of postnatal transmission of HIV is a fundamental question which plagues mothers / caregivers and policy makers.

As significant programmatic experience and research evidence regarding HIV and infant feeding have accumulated, a rapid advice based on revised principles and recommendations on HIV and infant feeding has been issued by the WHO in November 2009.[30,42] Tables 3.2.1 and 3.2.2 outline the new WHO recommendations for PMTCT and Table 3.2.3 outlines the other guidelines for PMTCT. Evaluation of efficacy and tolerance of preventive interventions complementary to antiretroviral prophylaxis such as HIV perinatal vaccine, passive immunoprophylaxis, micronutrient supplementation and vaginal-cervical disinfection by means of microbicides should be actively continued and encouraged. The challenge is to find the most cost-effective and feasible intervention to achieve zero percent transmission of HIV from an infected mother to her child and prevent millions of new pediatric HIV infections worldwide.

Pregnancy in Women with HIV-2 Infection

First described in 1986, HIV-2 is found mainly in West Africa, the epicenter of the epidemic being Guinea Bissau, where a prevalence of up to 10 percent has been reported[43] and in some areas of Southern India, Portugal, UK. Although HIV-1 and HIV-2 are related, there are important differences between them that influence pathogenicity, natural history and therapy. HIV-2 appears to be less readily transmitted than HIV-1 both sexually and from mother to child. HIV-2 differs from HIV-1 in its susceptibility to ART and also follows different mutation pathways to develop drug resistance. Pregnant women with detectable HIV-2 should be ideally managed using a HAART regimen to which the virus is sensitive.

Table 3.2.1: Eligibility criteria for ART or ARV prophylaxis in HIV infected pregnant women : The new WHO recommendation

CD4 count available	
CD4 ≤ 350 cells/mm^3	CD4 ≥ 350 cells/mm^3
ART regardless of clinical stage	ART if symptomatic (stage 3 or 4)
WHO clinical stage	
Stage 1	ARV prophylaxis
Stage 2	ARV prophylaxis
Stage 3	ART
Stage 4	ART

Source:http://www.who.int/hiv/pub/mtct/rapid_advice_mtct.pdf.

Table 3.2.2: ARV prophylaxis options recommended for HIV infected pregnant women who do not need treatment for their own health—new WHO recommendation

Option A	*Option B*
Maternal ZDV	Maternal triple ARV prophylaxis
Mother	***Mother***
• Antepartum ZDV (from as early as 14 weeks gestation) • sd-NVP at onset of labor • ZDV + 3TC during labor and delivery • ZDV + 3TC for 7 days postpartum • sd-NVP and ZDV + 3TC can be omitted if mother receives > 4 weeks of ZDV antepartum	Triple ARV from 14 weeks until one week after all exposure to breast milk has ended • ZDV + 3TC + LPV/r • ZDV + 3TC + ABC • ZDV + 3TC + EFV • TDF + XTC + EFV
Infant	***Infant***
Breastfeeding infant Daily NVP from birth until one week after all exposure to breast milk has ended *Nonbreastfeeding infant* ZDV or NVP for 6 weeks	*Breastfeeding infant* Daily NVP from birth to 6 weeks *Nonbreastfeeding infant* ZDV or NVP for 6 weeks

AZT: Zidovudine; 3TC: Lamivudine; NVP: Nevirapine; EFV: Efavirenz; TDF: Tenofovir; FTC: Emtricitabine; XTC: 3TC or FTC; LPV-r: Lopinavir/ritonovir; ABC: Abacavir;
Source: http://www.who.int/hiv/pub/mtct/rapid_advice_mtct.pdf.

Table 3.2.3: Recommendations for PMTCT as per different guidelines other than WHO, for mothers not requiring/ receiving ART for their own health

Guideline	*Prophylaxis for the mother*	*Elective cesarean section*	*Infant feeding*	*Prophylaxis for the newborn*
DHHS[7]	**Antepartum:** Initiation of HAART after 1st trimester with regimen chosen based on resistance testing (if detectable VL) and therapy history (ZDV and 3TC to be included as far as possible) **Intrapartum:** Continuation of chosen HAART + ZDV continuous IV infusion 2 mg/ kg over 1 hour followed by 1 mg/ kg/ hour until delivery **Postpartum:** Discontinuation of HAART (if NNRTI based regimen: Stop NNRTI at birth and continue NRTIs for 1 week and stop)	At 38 weeks, if Viral Load is unknown / more than 1000 copies/ ml	Complete avoidance of breastfeeds	ZDV 2 mg/kg bid for 4 weeks
Spain[25] (GESIDA)	**Antepartum:** Initiation of HAART after 14 weeks, with ZDV + 3TC and NVP (only if CD4<250 cells) or PI (SQV/r or LPV/r) **Intrapartum:** Continuation of chosen HAART + ZDV continuous IV infusion 2 mg/kg over 1 hour followed by 1 mg/kg/hour until umbilical cord section **Postpartum:** Stop HAART, if not indicated for mother's health (staggered interruption in NNRTIs). Adapt HAART, if indicated and simplification is an option	At 38 weeks, if Viral Load is unknown / more than 1000 copies/ml Consider if VL 50-1000 copies/ml	Complete avoidance of breastfeeds	ZDV 2 mg/kg bid for 6 weeks
UK[35] (BHIVA)	**Antepartum:** Initiation after 1st trimester (latest by 28 weeks) with a short-term ART regimen chosen based on resistance testing (if detectable VL) and prior therapy history; ZDV and 3TC to be included along with a boosted PI, unless there are any contra- indications **Intrapartum:** Continuation of chosen HAART + ZDV continuous infusion IV 2 mg/kg over 1 hour, followed by 1 mg/kg per hour until delivery **Postpartum:** Discontinuation of HAART (if NNRTI based regimen: Stop NNRTI at birth and continue NRTIs for 1 week and stop)	At 38 weeks, if Viral Load more than 50 copies/ml at 36 weeks	Complete avoidance of breastfeeds	ZDV 2 mg/kg bid for 4 weeks
NACO India[44]	**Antepartum:** nil **Intrapartum:** sd NVP 200 mg **Postpartum:** nil		Breastfeeding	sd NVP 2 mg/kg to the baby within 72 hours after birth

PI: Protease inhibitor; ZDV: Zidovudine; NNRTI: Nonnucleoside reverse transcriptase inhibitor; VL: Viral load; NRTI: Nucleoside reverse transcriptase inhibitor; sd: Single dose; NVP: Nevirapine; 3TC: Lamivudine; SQV/ r: Saquinavir/ritonovir; LPV/ r: Lopinavir/ritonovir.

NNRTIs and the fusion inhibitor enfuvirtide have no activity against HIV-2 and in the light of the current, albeit limited data, ZDV monotherapy should not be used. These factors make it more crucial that proper selection of, and adherence to the first antiretroviral combination regimen, is in place in order to achieve a successful treatment response. With regards to the mode of delivery, if the viral load is not undetectable/mother is symptomatic/has low CD4 cell count, an ELSCS could be planned at 38 weeks gestation.[35] With regards to breastfeeding, it is advisable to avoid this method of feeding, if feasible alternatives are in place.

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3.3

Prevention of *In Utero* and Intrapartum HIV: Mother-to-Child Transmission: The Safety and Efficacy of Antiretroviral Therapy

Graham P Taylor

Introduction

Whilst most attention was being paid to the risk factors of adults presenting in the early 1980s with the then newly described syndrome of acquired immunodeficiency (AIDS), less noted but equally important reports of AIDS occurring in children were published as early as 1984. Thomas et al reported the onset of AIDS at age five months[1] whilst Cowan et al reported three half-siblings, with *in vitro* and clinical evidence (PCP in two and cutaneous candidiasis in all three and the mother) of cellular immune defects and postulated mother-to-child transmission of the causative agent.[2] Maternal HIV infection through peripartum blood transfusion with subsequent transmission to her child through breastfeeding was documented in 1985.[3]

Globally heterosexual intercourse has been the dominant route of HIV transmission and 50 percent of infected adults are female and predominantly of childbearing age. Thus, as the epidemic spread and the number of infected adults increased year on year through a quarter of a century, pediatric infections ran a parallel course with an estimated two million children living with HIV in 2007.

Risk Factors Associated with HIV Mother-to-child Transmission

Since, even in the absence of interventions, not all children born to women infected with HIV become infected, identification of risk factors associated with transmission led to the avoidance of practices that might increase risk. However, as therapeutic interventions to reduce transmission have become increasingly successful, reappraisal of these risk factors has become important. This may be most important in settings where both highly active antiretroviral therapy and cesarean section are readily accessible and relatively safe.

Timing of Infection

HIV transmission may occur antepartum, intrapartum or postpartum and dissecting further the timing of infection allows appropriate use of interventions. Thus, if antepartum transmission was to occur primarily in the first trimester then many transmissions might occur even before pregnancy was diagnosed and before effective intervention could have been initiated. Human trophoblasts express CD4 and can be infected *in vitro* with HIV.[4] Infection of the placenta, at all stages of pregnancy including the first trimester[5] and fetal infection as early as gestational week 15[6] have been reported but no syndrome of congenital HIV infection has been described. In a study of aborted fetuses, infection was identified only in those that had been spontaneously aborted whilst induced abortions were uninfected, suggesting that infection was associated with disruption of the fetoplacental unit.[7] In general therefore, although infected with HIV, the placenta is for the most part an excellent barrier to infection of the fetus.

Study of infants born to HIV positive mothers reveals some to be already infected at the time of delivery, being HIV DNA PCR positive whilst others are initially HIV DNA PCR negative but become positive, despite no further risk for infection after delivery. Analysis of these findings has led to a model of the timing of infection which concludes that infection is rare prior to the 3rd trimester, that one-third of infections occur *in utero* during the two months prior to delivery and that approximately two-third of pregnancy related infections occur at the time of delivery.[8]

Postpartum infection occurs through exposure to untreated colostrum and breast milk. HIV can be cultured from breast milk and as with blood, HIV in breast milk can be detected both in the cells, which contain proviral HIV DNA,[9] and in the liquid component, in which HIV RNA can be detected and quantified.[10] Although the volume of colostrum is relatively small and the proportion of infected breast milk cells lower than in mature milk, the very high

number of breast milk cells in colostrum and early breast milk results in a much higher number of HIV infected cells/ml early in breastfeeding compared with later.[11] Whilst the volume of breast milk ingested increases, HIV RNA viral load has variously been reported to remain constant[12] or increase over time.[13] The net result is continuing exposure of the infant to HIV infection with the risk of infection accumulating throughout the duration of breastfeeding. The incidence of infection has been reported to be highest during the first five months of breastfeeding (0.7% per month), with marginally lower rates (0.6%) through to 11 months and much lower risk thereafter out to 17 months (0.3%)[14] whilst in a randomized infant feeding trial, 75 percent of breastfeeding related transmissions occurred during the first six months.[15] In one meta-analysis of data relating to infant feeding from clinical trials, almost two-third of breastfeeding related infection was attributed to early breastfeeding with 13 percent transmission among women who breastfed for up to two months compared with 21 percent among women who breastfed for 3 months or more.[16] However, another meta-analysis, using individual data from nine clinical trials, found a linear risk with 8.9 late postnatal infections per 100 breastfeeding years[17] (Fig. 3.3.1) graphically summarizes the timing of HIV mother-to-child transmission in the absence of any intervention.

HIV Viral Load

The single most important risk factor for HIV mother-to-child transmission in the absence of intervention is maternal HIV load, measured as HIV RNA copies per ml (cpm) plasma. This risk has been quantified in several studies that draw similar conclusions. Although only thirty women in the Women-Infant Transmission Study (WITS) had viral loads above 100,000 HIV RNA cpm, transmission occurred in almost two-thirds (63.3%) of these non-breastfeeding women.[18] Similarly in the European Collaborative Study (ECS), mothers with a viral load >100,000 HIV RNA cpm had a transmission rate of 41.7 percent.[19] Despite the correlation of risk with viral load in the ECS, no level of viral load below which transmission did not occur was detected. Whereas in the WITS, although overall the rates of transmission were higher, transmissions were not reported at less than 1000 HIV RNA cpm. Such differences may account for the differences in guidelines over the years with a generally more aggressive approach in Europe with the recommendation for a pre-labor cesarean section if HIV RNA is detectable despite combination antiretroviral therapy in the British HIV Association guidelines (2008),[20] compared with a cut-off at 1000 in the USA. A meta-analysis of seven North American and two European cohorts from the 1980s and early 1990s found a transmission rate of 5 percent when HIV viral load was less than 1000 cpm.[21] Although rare, 0.1 percent in the UK cohort, transmission have been reported even when the HIV viral load at delivery was <50 HIV RNA cpm. However, in at least two of the three cases, infection was presumed to have occurred prior to the initiation of highly active antiretroviral therapy (HAART).[22] HIV viral load was reported to be the only significant risk factor for mother-to-child transmission in a study from Southern Brazil[23] and has also been reported to be important in a Thai study where a viral load >35,000 HIV RNA cpm was independently associated with *in utero* transmission with an adjusted odds ratio (AOR) of 4.2. The risk was even greater with intrapartum HIV-transmission with an AOR

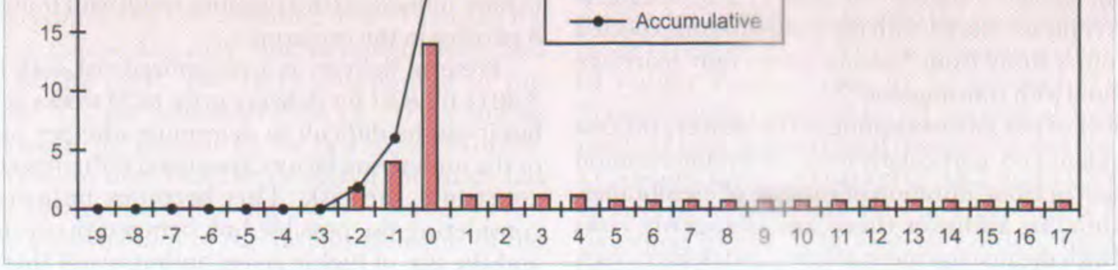


Fig. 3.3.1: The timing of HIV mother-to-child transmission in the absence of any intervention

of 7.1 for viral loads above this figure.[24] Transmission risk of HIV-2 is also related to viral load with the risk (OR) increasing 2.9 fold with each 1 log increase in viral load in a study from the Gambia. Interestingly, the fold increase in risk was the same for both HIV-1 and HIV-2 despite the overall much lower rate of transmission of HIV-2 (4%) compared with HIV-1 (24.2%).[25]

The degree of immune impairment of the mother has been associated with risk of HIV mother-to-child transmission both using clinical and immunological criteria. Thus, an early French cohort have had an AIDS defining illness (CDC Stage IV), relative risk (RR) 1.9 compared with the asymptomatic state and CD4 lymphopenia were associated with transmission. For the latter, the lowest rate of transmission was seen in mothers with CD4 lymphocytes greater than 600 cells/μl (15%) and highest when the CD4 cell count was less than 200 cells/μl (43%). This study predated measurement of HIV-viral load and the degree of viremia was therefore characterized as either HIV p24 antigen positive (equating to high viral load) or negative. In the multivariate analysis, p24 antigenemia and maternal age were found to independently predict risk.[26] In the WITS, analysis of data from participants between 1990 and 2000 found low CD4 lymphocyte percentages to be associated with intrapartum (OR 1.7 95% confidence intervals 1-2.8) but not *in utero* transmission risk.[27] In an ECS analysis from the pretreatment era even a CD4 lymphocyte count of less than 700 cells/μl was associated with the risk of transmission[28] along with p24 antigenemia, with the implication that risk associated with lower CD4 cell counts is not necessarily due to opportunistic infections. However, in later years, following the advent of interventions, CD4 count or percentage *per se*, is no longer associated with risk.[29] In the New York City Perinatal HIV Transmission Collaborative Study, transmission risk was not found to correlate with HIV related illness, although a history of inpatient treatment for pneumonia during the 12 months prior to delivery was.[30] In the Congo, having symptoms of HIV-1 infection during pregnancy was associated with a ten-fold increased risk of transmission (10.3, 95% CI 2.9-37.1).[31] In this study of 118 HIV- exposed infants, the duration of the mother's relationship with the infant's father, if less than 1 year, carried a similar risk (OR 11.1 95% CI 2.4-50.2). This contrasts starkly with the somewhat unexpected finding from a study from Nairobi where only marriage was associated with transmission.[32]

A number of risk factors relating to the delivery process have been identified, particularly from the preintervention era: duration of labor, duration of rupture of membranes, bloody labor. In addition there are iatrogenic risks associated with the management of labor and delivery such as fetal scalp electrodes and fetal blood sampling and these are thus avoided in the management of women with HIV infection. It is worth noting however that in an analysis of the ECS from 1984-91, i.e. prior to routine intervention other than avoidance of breastfeeding, the risk associated with iatrogenic factors for transmission: episiotomy, fetal scalp electrodes, forceps delivery and vacuum extractions, were only observed in the centers that did not routinely use these measures.[33] These findings were based on data from 721 infants and the overall transmission rate of only 14.4 percent is also noteworthy, being lower than that reported during the same era from Europe (~20%) or the USA (25%) amongst non-breastfeeding women. In the WITS data, from 525 women–infant pairs found rupture of amniochorionic membranes for more than four hours to more than double the risk of transmission and that this risk occurred regardless of the final mode of delivery.[34] By definition, cesarean sections were occurring after variable periods of membrane rupture with or without labor. In the untreated mother, the risk of HIV transmission increases with the duration of rupture of membranes at a rate of 2 percent per hour.[35] These data are based on an individual data meta-analysis of 4721 deliveries occurring prior to 1997 and restricted to women with up to 24 hours rupture of membranes. The risk of acute chorioamnionitis increases with the duration of rupture of membranes. In a nonrandomized study of vaginal lavage, a study period with no intervention followed by a period with the intervention, manual cleansing with 0.25 percent chlorhexidine solution at presentation and every 4 hours during labor, did not reduce transmission. However, in a sub-group analysis, the rate of transmission was significantly lower in treated women (25% v 39%) if membranes had been ruptured for more than four hours.[36] Furthermore, other benefits were reported with reduced neonatal admissions due to sepsis, reduced neonatal deaths as well as reduced maternal admissions postdelivery, particularly those related to infection.[37] A decade later the same group studied the effect of three courses of systemic therapy with erythromycin and metronidazole during the second and third trimesters of gestation and metronidazole plus ampicillin intra-partum on HIV transmission. However, this approach reduced the incidence of neither chorioamnionitis nor HIV transmission.[38] As will be discussed below the universal use of single-dose nevirapine to reduce the risk of mother-to-child transmission is likely to have influenced this negative result with transmission 7-8 percent in the two arms.

Preterm delivery is a recognized risk with odds ratio 3.80 (1.62-8.91 for delivery prior to 34 weeks gestation),[39] but it can be difficult to determine whether prematurity or the underlying factors associated with preterm delivery constitute the risk. This becomes important when considering the possible link between pre-term delivery and the use of highly active antiretroviral therapy. Thus factors associated with preterm delivery such as bacterial vaginosis may in addition be linked with chorioamnionitis.

Female gender is associated with a small but significant increase in rates of transmission but this is only seen if the analysis is restricted to babies born by cesasean section.[40] This suggests that there is both an increased risk of earlier *in utero* transmission for females and of later *in utero* or intra-partum risk for males. The reasons for these findings are uncertain. Twin pregnancy *per se* might be considered a risk factor for transmission with one or both twins infected in the 28.3 percent of twin pregnancies, during the pre-HAART era, compared with 13.5 percent for singleton pregnancies.[41] Much has been learnt about other risks from studies of twins. Thus transmission to the first-born twin is considerably more frequent than to the second. Data from the International Registry of HIV exposed Twins reveals a hierarchy of risk: First-born vaginal delivery (35%), first-born cesarean section (16%), second-born vaginal delivery (15%) and second-born cesarean section (8%).[42] This risk may be due to longer time to passage the birth canal of the first born with this journey likely to be more traumatic. Further analysis of these data attributes 76 percent of the transmission risk to vaginal exposure. The observation that second-born twins, despite being delivered by cesarean section, are still at risk of HIV infection, is however an indication that passage through the birth canal and exposure to infected maternal blood and amniotic fluid either through mucus membranes or tiny breaches to the skin, does not account for all transmission risk.

Interventions to Reduce the Risk of HIV Mother-to-Child Transmission

Three key randomized controlled studies revolutionized the management of HIV infection in pregnancy, since when further developments bring us to the current situation whereby, essentially, with rare exceptions, all HIV-transmissions from mother to child are, given the right resources, preventable.

The AIDS Clinical Trials Group study 076, examined the potential of, the then only available antiretroviral therapy, azidothymidine (AZT), also known as zidovudine (ZDV) to reduce HIV mother-to-child transmission.[43] Participants were randomized to either ZDV 100 mg five times daily or placebo from the end of the first trimester. Following the initiation of labor an intravenous infusion of ZDV was commenced with a loading dose of 2 mg/kg for the first hour followed by ZDV 1mg/kg until delivery and clamping of the cord. The third component of the intervention was the administration of ZDV 2 mg/kg every six hours to the neonate for the first six weeks of life. It is important to note that the design of the study has influenced management for almost two decades even though the contributions of the various elements of the intervention have not been completely quantified. Zidovudine monotherapy reduced transmission by 67.5 percent, from 25.5 to 8.3 percent, in a non-breastfeeding population with CD4+ lymphocyte counts greater than 200 cells/μl, despite only reducing median viral load by 0.24 log10 by the time of delivery, with viral load reduction not found to be associated with transmission risk in the zidovudine treatment arm.[44]

Whilst some observational studies suggested that the risk of HIV transmission could be reduced by cesarean section, this was not a universal finding, perhaps due in part to different practices and indeed different understanding of what is meant by an elective cesarean section (ECS). The introduction of the term, prelabor cesarean section (PLCS), which more precisely refers to a prelabor, pre-rupture of membranes, cesarean section distinguished this intervention from the previously used ECS which could in theory include any planned, or elective, CS even if this was performed after the initiation of labor. Generally more cesarean sections were being undertaken in Western Europe specifically to reduce the risk of HIV transmission than in North America. The second sentinel study that fundamentally changed practise in many centers, particularly in Europe, was the International Mode of Delivery Study. HIV infected women were recruited over a five-year period and randomized at gestational week 36 to either a spontaneous vaginal delivery or PLCS. In this study of 370 randomized mother-infant pairs, PLCS reduced transmission, in women who reached term, by more than 80 percent from 10.7 to 1.7 percent. Furthermore, because the study was conducted from 1993, prior to the results of ACTG 076 in November 1994 and after which zidovudine was recommended for all participants, to 1998, the study, or at least the analysis, evolved into a multifactorial design. Thus, in a posthoc analysis, four groups could be defined, those who had no intervention, those delivered by PLCS with no additional intervention, those who randomized to spontaneous vaginal delivery and who took ZDV and those who delivered by PLCS and took ZDV. With no intervention transmission was 19.5 percent, with PLCS alone 3.9 percent, with ZDV alone 4.3 percent and with PLCS plus ZDV 0.8 percent, establishing this combined intervention as the gold-standard.[45]

A meta-analysis of 15 prospective studies, ten from North America and five from Europe also contributed to the resolution of the conflicting data from observational studies, with similar findings to the randomized controlled mode of delivery study. Elective cesarean section was shown to reduce transmission by 55 percent (Fig. 3.3.2). Transmissions occurred to 7.3 percent of infants whose mothers took antiretroviral therapy but did not deliver by ECS whilst the combination of ART and ECS resulted in an overall transmission rate of 2 percent, a 85 percent reduction in risk.[46] In western Europe, the PLCS rate increased from 16 percent prior to 1994 to 61 percent in 1999-2001, but even here striking regional differences are

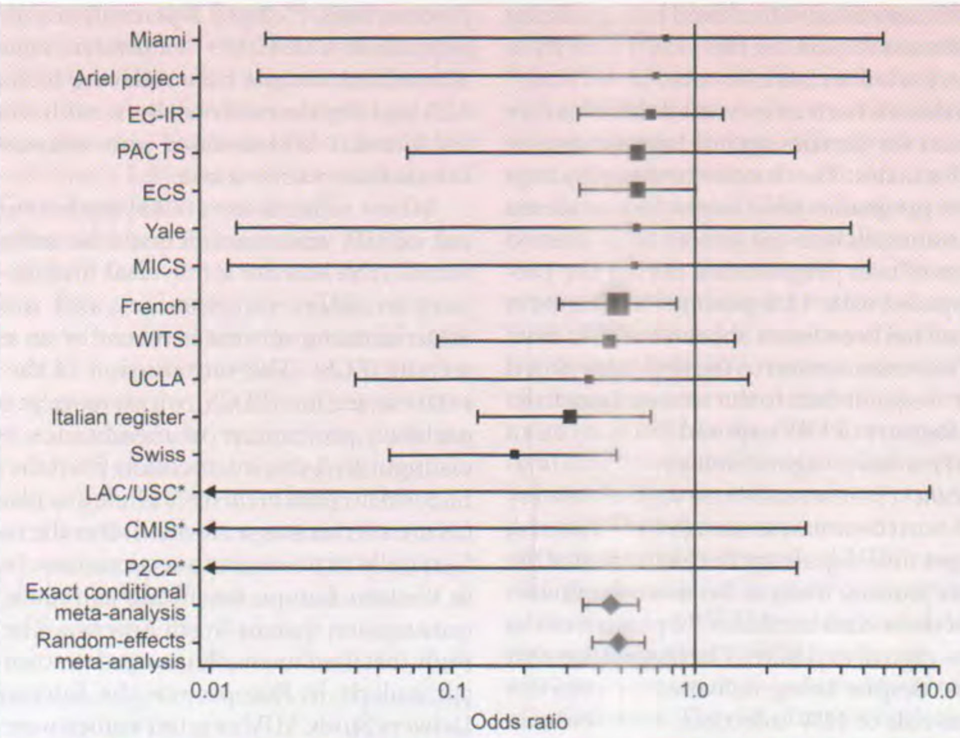


Fig. 3.3.2: Result of meta-analysis of efficacy of PLCS - published by International Perinatal HIV Group. N Engl J Med. 1999;340:977-87. Reproduced by permission of the Massachusetts Medical Society

noted with the highest PLCS rates found in Italy and Spain. The most recent time interval studied, 2005-2007, shows PLCS rates to be decreasing.[47] This is likely to reflect, as discussed below, increasing confidence in HAART alone, to prevent MTCT, when maternal viral load is undetectable (i.e. <50 HIV RNA cpm).

The third, practise-modifying study, was a randomized, controlled study of a single dose of nevirapine given to the mother in labor and to the neonate 48-72 hours after delivery, compared with intrapartum zidovudine, the HIVNET 012 study.[48] Nevirapine, a non-nucleoside reverse transcriptase inhibitor, is rapidly absorbed and so efficiently crosses the placenta two hours post ingestion, plasma concentrations in cord blood are sufficient to inhibit viral replication, the concentration of 1000 mg/l being 100-fold higher than the inhibitory concentration of wild type HIV-1. Furthermore, clearance, especially in the first days of treatment before nevirapine induced liver enzyme induction, is particularly slow. Thus, in HIVNET 006, a pharmacokinetic study, a single 200 mg dose of nevirapine (sdNVP) given to the mother in established labor followed by single 2 mg/kg dose to the baby at 72 hours resulted in nevirapine concentrations greater than 100 µg/l for 7 days.[49] The median half-life of nevirapine in the women was 60 hours and in the neonate after the 72 hours dose, 46 hours. These data, and early PK studies in the USA, provided the rationale for the HIVNET 012 study. With zidovudine already proven to reduce HIV mother-to-child transmission, a placebo-arm would not have been ethical, hence the comparator arm of zidovudine given to the mother during labor and to the infant for 1 week. Although, the efficacy of zidovudine given so late had not be proven in an RCT, observational studies had suggested some benefit, whilst the standard of care in Uganda, the study site, did not include antiretroviral therapy. At age 4-6 weeks, 21.3 percent of babies exposed to zidovudine were HIV-1 infected, whereas in the nevirapine arm, 11.9 percent were infected, a reduction in transmission of 44 percent. This also held true at 13-16 weeks, with transmission rates of 25.1 percent and 13.1 percent in the two arms, a 47 percent reduction.

The initial studies of ZDV monotherapy (ZDV_m) in the USA and in Thailand were conducted amongst women who were able to avoid breastfeeding. Whether the benefits of antiretroviral therapy during pregnancy and/or labor in a population where the infants would then be exposed to HIV through breastfeeding for many months were not known. So it was important and reassuring to learn from both HIVNET 012 and studies of ZDVm in Africa that despite postnatal HIV transmission through breastfeeding, the benefits of therapy to reduce *in utero* and intrapartum transmission could still be seen at age 18 months. Figure 3.3.3 illustrates this with a graphical representation from two ZDVm studies in West Africa, the DITRAME[50]

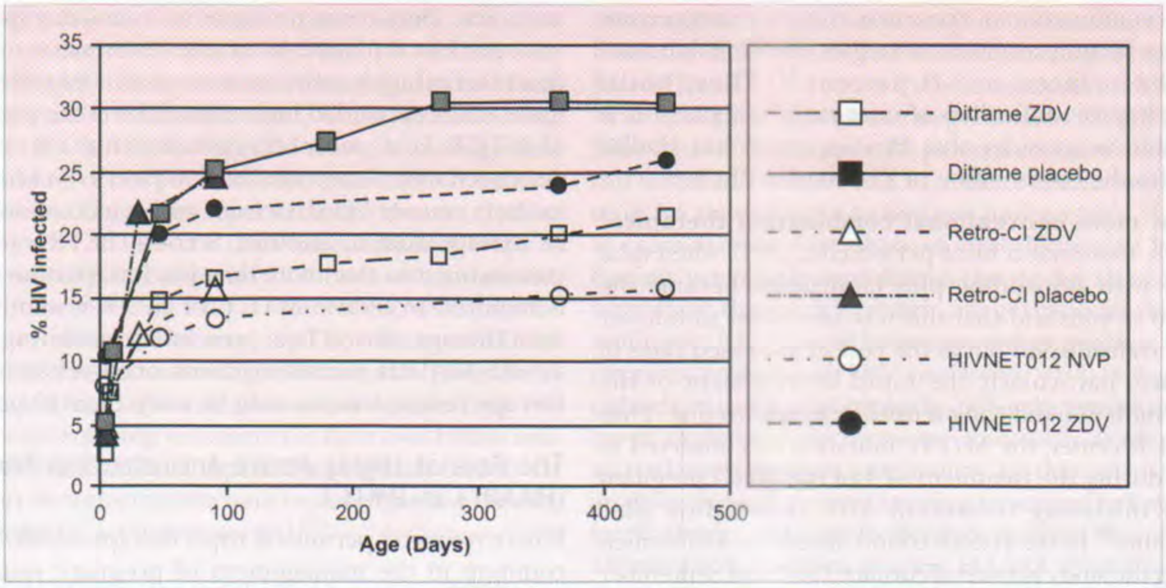


Fig. 3.3.3: HIV transmission rates with ZDVm (broken-lines) compared with placebo (solid lines) and of IP/PP NVP (dotted line) vs ZDV (dot-dash)

and Retro-CI studies[51] as well as the sdNVP, HIVNET 012, study from Uganda.[52]

These three studies, ACTG 076, HIVNET 012, and the International Mode of Delivery study each fundamentally shifted the goal posts in the prevention of HIV mother-to-child transmission. ACTG 076 by demonstrating the efficacy of even a single antiretroviral agent and reducing transmission rates to single figures. HIVNET 012 by providing an intervention that, by nature of its simplicity and relative cheapness, could be offered broadly, even in resource-limited settings. The mode of delivery study, not only by demonstrating that 80 percent of transmission could be prevented by PLCS, with implications for our better understanding of the timing of delivery, as well as being the single-most effective intervention available at that time to prevent intrapartum transmission, but also by nature of the post-hoc analysis of PLCS with ZDV setting a gold-standard of care, resources permitting, with the potential to reduce transmission to less than 1 percent. It is perhaps a measure of how fast the field of HIV medicine moves that, in 2010, all of these interventions are fast becoming just footnotes in the history of PMTCT.

It is also salutary to consider whether, if we had known then (when the studies were initiated) what we know now, ACTG 076 or HIVNET 012 would have ever been conducted. ACTG 076 recruited from April 1991 to December 1993. Fischl's report of the efficacy of zidovudine to improve short-term survival in patients with advanced HIV infection was published in 1987.[53] The benefit of therapy with zidovudine on survival was such that the study, planned for 24 weeks, was terminated early, by which time only 27 of the 282 subjects had completed 24 weeks. The next several years saw many publications on zidovudine monotherapy with various messages culminating in the results from Concorde,[54] and ACTG,[55] large randomized placebo controlled studies that failed to show clinical benefit despite up to three years therapy in asymptomatic patients starting therapy. We know now of course, that zidovudine monotherapy is not effective in the treatment of HIV infection, apart from the short-term effect that Fischl and her colleagues demonstrated, and understand the mechanisms of treatment failure. Many argue now that there is no longer a place for ZDVm in PMTCT too, despite the proven efficacy, a 67 percent reduction with the full ACTG 076 protocol, or a 50 percent reduction with a shorter course and no infant dosing, as per the Thailand study.[56] Similarly, one can consider the HIVNET 012 study in the light of current knowledge concerning the emergence of mutations associated with resistance to the current members of this class of therapy following a single dose of nevirapine to the mother for PMTCT, clearly a problem associated with this intervention that was not considered at the design stage. This is not to be critical of the studies but to contemplate whether we would have been deprived of both interventions which have to date prevented a multitude of HIV transmission and were in their time, and perhaps still are in some situations, the only available options.

With the success of ACTG 076 and other ZDVm studies and the efficacy of sdNVP intrapartum, the natural next step was to combine the two approaches. The data from Thailand using the standard Thai shorter course of ZDVm (from 36 weeks) plus intrapartum sdNVP demonstrated that

with the combination of these two, relatively inexpensive and more broadly available strategies, transmission rates could be reduced to 1.9 percent.[57] Thus, whilst recognizing the difficulties of inter-study comparison, it is possible to consider that this approach has similar efficacy to the combination of ZDVm plus PLCS.

What of more conventional combination therapies? Certainly there was a brief period circa 1997 when dual therapy with zidovudine plus lamivudine became the standard of care and that this was associated with lower rates of transmission but at the cost of increased rates of resistance, particularly the rapid development of the M184V mutation reducing sensitivity to lamivudine. Thus in one UK center, the M184V mutation was observed to appear during the treatment of 4 of the first 5 pregnant women initiating treatment with zidovudine plus lamivudine.[58] In the French cohort study, the 445 women entering the study between February 1997 and September 1998 were treated with zidovudine as per the ACTG 076 protocol with the addition of lamivudine at gestational week 32. Transmission was 1.6 percent compared with 8 percent in the historical controls treated with zidovudine alone. The median reduction in viral load, 1.24 log 10 HIV RNA copies/ml plasma, was also greater than reported previously for ZDVm, just 0.3 log10 by the time of delivery in ACTG 076, but in 52/132 (39%) women, the M184V mutation was detected at 6 weeks postpartum.[59] Short course zidovudine plus lamivudine from 34 weeks gestation was also reported to be safe and effective in an open study from Thailand, with a reduction in viral load by delivery of 1.55 log10 and a 2.8 percent transmission rate.[60] Whilst in the PETRA study, from Tanzania, South Africa and Uganda, three zidovudine plus lamivudine arms, to investigate the efficacy of therapy at different times were compared with placebo. In the most effective arm, zidovudine plus lamivudine commenced at 36 weeks gestation, with intrapartum dosing every 3 hours and postpartum treatment continued for 7 days, the transmission rate at age 6 weeks was 5.7 percent [relative risk (RR) 0.37 95% CI 0.21-0.65] compared with 15.3 percent with placebo. Intrapartum (IP) oral dosing alone had no significant effect on transmission [14.2%, RR 0.93 95% CI 0.62-1.4] whereas IP plus post-partum (PP) treatment for 7 days significantly reduced transmission to 8.9 percent [RR compared with placebo 0.58 95% CI 0.36-0.94].[61] Not all dual therapy was better than ZDVm, with the combination of stavudine plus didanosine faring no better than ZDVm in terms of transmission risk reduction despite a far superior effect on viral load suppression (1.9 log10 compared with 0.76 log10).[62] Based on what we know of the pharmacokinetics of the three compounds, the most logical explanation for this discrepancy in effect is the better transplacental transfer of ZDV compared with either didanosine or stavudine. Despite the problems with dual therapy, which was quickly replaced by triple therapy, soon to be described as highly active antiretroviral therapy (HAART), these studies provided important data on the prevention of MTCT. First, more effective antiviral effect can be associated with better transmission rates even when given in short courses but data from one combination cannot be extrapolated to another. Second, PETRA provided convincing data that more than just intrapartum therapy is required to reduce MTCT, or to see it another way, even therapy started late, even as late as during labour, as with NVP, can if combined with one week of neonatal therapy reduce transmission by more than 40 percent.

The Role of Highly Active Antiretroviral Therapy (HAART) in PMTCT

Where resources permitted, triple therapy rapidly became common in the management of pregnant women for several reasons: pregnant women required such therapy for their own health, dual therapy was not sufficiently effective and associated with resistance, ZDV monotherapy even with PLCS would not abrogate all risk especially where the baseline viral load was high and later, increasingly, conception whilst on HAART. Consequently data gradually emerged on the efficacy of HAART from observational studies. A North American prospective cohort study of women enrolled prior to July 2000 reported a transmission rate of 1.2 percent (95% CI 0-2.5%) with protease inhibitor based HAART.[63] Whilst considerably better than the 10.4 percent transmission rate reported with ZDVm in the same cohort, it should be noted that this rate of transmission was similar to that observed with zidovudine monotherapy plus either maternal and neonatal single dose nevirapine (1.1%) or PLCS (0.8%).

Similar results were reported from Western Europe. By 2001-2003, at which time 92 percent of women in the European Collaborative Study were taking HAART during pregnancy, the transmission rate had fallen to 0.99 percent (95% CI, 0.32-2.30%).[64] Since zero transmission was still not achieved and given the efficacy of sd nevirapine alone, the PACTG 316 study of the addition of the two dose nevirapine strategy to existing antiretroviral therapy, including HAART was a logical progression. However, nevirapine failed in this setting to further reduce transmission and the overall transmission rate remained around 1 percent, in this study 1.5 percent. The participants in this study, from Europe and the Americas, included a significant number of women (28%) on zidovudine monotherapy for whom the addition of nevirapine would have been expected to provide additional protection but 34 percent of all women delivered by ECS.[65] With the roll-out of access to HAART in low and middle income countries further successes have been reported such as the Drug Resource Enhancement for AIDS and Malnutrition

(DREAM) program in Mozambique which has also achieved transmission rates of between 1-2 percent with maternal HAART for up to 6 months postpartum.[66] Data from National Surveillance in the UK and Ireland during the period 2000-2006 further add to our knowledge and understanding of the potential of interventions to reduce transmissions. Key points reported in 2008 were: (1) The importance of at least 14 days antepartum therapy – transmissions 0.8%; (2) The very low rates of transmission (0.1%) if maternal viral load is <50 HIV RNA copies/ml plasma at the time of delivery; (3) The efficacy of ZDVm plus PLCS when used according to British HIV Association guidelines, which advocate this as an option only for mothers not requiring treatment for their own health and with a baseline viral load repeatedly less than 10,000. In this cohort no transmissions were reported among the 464 mother-infant pairs thus managed.[67]

What to do if the Maternal Viral Load is <1000 HIV RNA Copies/ml Plasma at Delivery?

Data from several sources indicate transmissions occur even at low copy number. In a meta-analysis of 7 prospective studies from Europe and USA, transmission rates depended on ARV exposure. Thus in untreated mothers the transmission rate was 9.8 percent (95% CI, 7.0-13.4%) whilst treatment during pregnancy and/or delivery reduced transmission to 1.0 percent (95% CI 0.4-1.9%).[68] In this population, cesarean section was still associated with a lower (relative risk 0.3) rate of infection. In the European Collaborative Study, delivery by PLCS further reduced transmission risk by 90 percent (odds ratio, 0.10; 95% CI, 0.03-0.33) among the 560 mothers with undetectable viral loads (<50, <400 or <1000, according to the era and assay used).[69] Patterns of practice continued to vary and with growing confidence in HAART to reduce transmission to very low rates, many healthcare professionals have started to modify practice and will now routinely recommend a vaginal delivery if the maternal viral load is <50 HIV copies/ml plasma, at about week 36, when the final decision on mode of delivery is usually made. This is reflected in the changed patterns of mode of delivery that have been documented in Europe which in turn have given rise to the data that support this approach. Thus data from the UK and Ireland surveillance show that PLCS does not further reduce the transmission rate in mothers on HAART.[70]

Optimal Timing and Class of HAART

It is clear from the data above that the majority of transmission events are preventable, provided appropriate treatment/prophylaxis is given. In the UK and Ireland cohort, a risk factor associated with transmission was less than 14 days treatment prior to delivery. Also, there was evidence, in some rare cases of transmission despite HIV viral load <50 cpm at delivery that transmission had occurred prior to treatment.[71] Data from the ECS reveal that women starting nevirapine-based HAART were more likely to reach an undetectable viral load than women starting PI-based HAART (1.54 95% CI 1.05-2.26), only 73 percent of women achieved this target and women on a PI, most commonly nelfinavir, took 1.4 times longer to become undetectable.[72] Bell et al examined the first phase of viral decay with HAART during pregnancy and found this to be steeper with nevirapine than with lopinavir soft gel capsules than with nelfinavir.[73] Read et al have shown that treatment naive pregnant women with HIV viral loads >100,000 cpm are unlikely to reach <50 copies by 36 weeks gestation, when mode of delivery decisions are frequently made, unless started very early in pregnancy. In this retrospective analysis, only 20 percent starting treatment before 20+3 weeks reach <50 cpm by delivery and this figure fell to 10 percent for women starting HAART after this point. In this study, nevirapine-based HAART performed better than PI-based HAART at higher viral loads.[74] Therefore women with high viral loads should be commencing treatment early in the second trimester and CD4 count permitting nevirapine might be considered ahead of a PI.

When is it too Late to Initiate Prophylaxis?

Data from HIVNET 012 clearly indicates that considerable benefit is gained from prophylaxis, with a suitable compound such as nevirapine, even when initiated in labor. There are also data that support the use of sdNVP to the infant even in the absence of a maternal dose.[75,76] Data pertaining to ZDVm indicate a protective benefit, provided initiated no later than 48 hours postpartum.[77] There are no data refining this further and it is likely that there are intermediate reductions in protection, the longer the period from exposure to initiation to therapy. Therefore, a commonsense approach for late presenters, women in labor, is to initiate oral therapy with sdNVP, prior to establishing the IV zidovudine infusion, if available, or giving oral zidovudine with the nevirapine and treating the infant as below, except if only one further dose of NVP is to be used, this should be delayed to 72 hours. If delivery has already occurred the infant should receive zidovudine and nevirapine as soon as possible, and certainly aiming for less than 4 hours. It is however our practice to initiate a short course of HAART, usually zidovudine and lamivudine for 4 weeks with daily nevirapine for 2 weeks, relying on the longer treatment with zidovudine and lamivudine to cover the nevirapine tail.

Safety of Interventions to Reduce MTCT

As described above, the tools are now available to virtually eliminate the risk of MTCT and whilst many would argue

that HAART should be recommended to and provided for all pregnant women regardless of health, CD4 cell count and viral load, this is not yet universally available. It is therefore re-assuring that cheaper, simpler regimens can still offer significant risk reduction. Until now we have only considered the efficacy of interventions. Safety and acceptability are clearly highly important considerations in PMTCT as in the management of HIV infection. Of the first three nucleoside analogs, dideoxycytidine is no longer available due to its much greater toxicity compared with zidovudine, didanosine, lamivudine, whilst both indinavir and ritonavir have been superseded by better tolerated protease inhibitors.

Zidovudine is known to be myelotoxic and associated anemia and neutropenia. It is the former that tends to generate more concern during pregnancy especially in areas where profound anemia due to a multitude of causes, infectious and dietary, is common. The *in utero* and short neonatal exposure to zidovudine is also associated with anemia in the infant, but this is generally self-limiting and rarely is interruption of the neonatal prophylaxisconsidered. So to with the neutropenia seen in the babies—documented but rarely of clinical significance even though relative neutropenia can persist out to age18-24 months. Many of the clinically important toxicities seen after long-term and/or high dose zidovudineexposure are mediated by mitochondrial toxicity. The report therefore from the French cohort of two deathsattributed to mitochondrial encephalopathy, along with other cases, both clinically apparent and asymptomatic in, zidovudine +/- lamivudine exposed, HIV exposed but uninfected, children naturally caused considerable concern.[78] Two major approaches to explore further this important observation have been followed. The retrospective review of large cohorts for evidence of similar pathology have failed to identify similar cases.[79,80] Pathophysiology studies of mitochondrial depletion, particularly in PBMCs, have given mixed results with some evidence of mitochondrial depletion with both HIV infection and with zidovudine monotherapy (ZDV_m),[81] but not with HAART, whilst Cote et al found increased mitochondrial DNA but decreased mitochondrial gene expression with perinatal zidovudine exposure.[81,82] Various animals have reported mitochondrial toxicity related to zidovudine exposure in cardiac tissue[83,84] and brain.[85] A long-term prospective study of children exposed perinatally to ARV has found no evidence of cardiac disease out to 48 months[86] but in this study the children had been exposed to HAART during pregnancy rather than ZDVm or dual zidovudine plus lamivudine.

Whilst lack of evidence of harm is not the same as proof of safety, reported clinical events related to perinatal zidovudine +/- lamivudine exposure, linked mitochondrial toxicity remain rare and the balance of risk and benefit has to date strongly favored benefit. Thusfollowing their case note review of participants in the Pediatric Spectrum of HIV Disease Project, the authors noted the healthy survival of the large number of zidovudine exposed, HIV-1 exposed uninfected children compared with HIV-1 infected children. Long-term surveillance of ARV-exposed HIV uninfected children is required not only to address particularly the question of mitochondrial toxicity but other potential long-term risks such as cancer and this applies to all therapies and all combinations. Herein also lies the problem. Follow-up of HIV exposed, uninfected children has proven to be difficult, particularly past the age of sero-reversion, for many reasons including disclosure and inconvenience. Prospective cohort studies will inevitably have recruitment bias and the number of actual combinations of ARVs are becoming ever more numerous, whilst the differing durations and timings of exposure add to the complexity. Enrolment of children into a drug exposure registry with cross-referencing to other national registries, such as a cancer registry, could in the long-term provide valuable data but re-consenting at the age of majority would remain a challenge.

The major safety issues relating to nevirapine are the incidence of Stevens-Johnson Syndrome and of drug-induced hepatitis. Both are known to occur more readily in females than in males and are less common at lower CD4 counts. Deaths due to these toxicities have been reported and careful monitoring of the initial therapy (particularly the first eight weeks) is essential. Although severe nevirapine toxicity has been reported among pregnant women[87,88] a number of studies have suggested that, nevirapine-related toxicity is at worst no more frequent in pregnant women than in nonpregnant women and at best may be less frequent.[89,90] Given the CD4 restrictions of nevirapine use and the new WHO guidelines for starting therapy in adults, HAART-based nevirapine should no longer be used for PMTCT and will only be initiated in pregnant women requiring treatment for their own health, with a CD4 count less than 250 cells/µl. Single-dose nevirapine has now been widely prescribed to women regardless of CD4 counts without any adverse health signal. Similarly sdNVP given to the baby at 72 hours has been well tolerated. Recent data, from a study of prevention of HIV infection during breastfeeding indicate that infant nevirapine extended to age six months remains safe.[91] Thus it seems that the immaturity of the infant immune system protects against significant nevirapine toxicity.

Whilst protease inhibitor based HAART has been associated with an increased incidence of gestational

diabetes, this has not been substantiated in subsequent studies.

Whether HAART is associated with an increased risk of pre-term delivery (PTD-delivery before 37 weeks gestation) has been and remains the most contentious PMTCT safety issue. The initial report from Switzerland, based on only 37 pregnant women exposed to combination therapies was followed by a combined report between the Swiss Cohort and the European Collaborative study.[92] Together these studies included 3920 mother-infant pairs with an overall preterm delivery rate of 17 percent. Compared to no antiretroviral therapy, ZDVm had no effect on PTD, combination therapy without a PI increased the risk by 1.82 (95% CI, 1.13-2.92), whilst combination therapy with a PI increased the risk by 2.60 [95% CI, 1.43-4.75]. Other factors associated with prematurity were advanced immune suppression and injecting drug use.[93] Being published in 2000 the majority of women in the study were untreated and only 108 took PI-based HAART. The next analysis from the ECS had similar findings demonstrating an increase in PTD over time, which paralleled the increasing use of HAART. By 2000-2004, 24.9 percent of deliveries in the ECS were preterm. In multivariate analyses being already on therapy prior to conception was associated with an increased risk of PTD (AOR 2.05 95% CI 1.43-2.95).[94]

Meanwhile colleagues in North America were reporting a different picture. Data from singleton pregnancies registered in the WITS and delivering between 1990 and Feb 2002 were analyzed. Treatment was classified into one of four types: (1) Zidovudine monotherapy and combination therapy including zidovudine; (2) Treatment with an NNRTI other than ZDV; (3) Any PI and (4) Any NNRTI. The timing of drug exposure was classified as either 'early' or 'late'. Early treated women were already on treatment by week 25. Late treated women had not received treatment by week 25 but had commenced treatment by week 32 or by delivery or had delivered prior to week 32. Severe PTD occurred in 4 percent and altogether PTD occurred in 18 percent. Prior PTD was less common in patients receiving monotherapy (mostly ZDV) than in untreated patients and more common in those on combination ART or HAART. However women on HAART were much less likely to be IDU, to smoke and had lower rates of genital tract infections including bacterial vaginosis. The major finding of this study was that 'late' initiation of ART that included ZDV was associated with a 50 percent reduction in PTD (OR 0.5, 95% CI: 0.3-0.8). It is difficult to interpret the observation that regimens containing nucleoside reverse transcriptase inhibitors other than ZDV were associated with a decreased risk of severe PTD, i.e. delivery prior to 32 weeks.[95]

However, it is important that the message of the study, that pregnancy outcomes in general were improved with ART compared with no therapy and that the risk benefit continues to favour the use of ART in pregnancy should not be obscured. In addition data from 11231 participants in the Pediatric Spectrum of HIV Disease (PSD), recruited between 1989 and 2004, showed a reduction in low birth weight from 35 to 21 percent and in PTD from 33 to 22 percent over this time. Multivariate analysis identified many independent risk factors for PTD: illicit drug use, lack of any antiretroviral therapy, black ethnicity, symptomatic maternal HIV infection and the study concludes that PTD rates (and low birth weight) declined during this period of increasing maternal antiretroviral therapy despite trends in the opposite direction in the general population. However, use of PI based HAART was associated with PTD.[96]

Martin et al analyzed the pregnancy outcomes of all patients attending a single UK center from 1995-2006. Since this post dates the introduction of ZDVm for PMTCT, only comparisons between therapies could be made. In the initial crude analysis, the following rates of PTD were observed: ZDVm 3/52 (5.8%); any HAART 25/156 (16%) with the ZDVm PTD rate no different from the background rate at the center. More detailed breakdown of these rates revealed an association with the timing of HAART, rather than indication for HAART. Thus, the PTD rate for women already on HAART at conception was 9.8 percent whilst for those initiating HAART during pregnancy, the PTD rate was 22 percent, regardless of whether they met the criteria to start therapy for maternal health (CD4 < 200 at that time) or took short-term HAART for PMTCT.[97] These data are completely at odds with a study from Brazil that found 20.2 percent rate of PTD with pre-conception HAART compared with only 10.2 percent with HAART initiated during pregnancy and found little difference between ZDVm (11.7%) and HAART (13.1%).[98]

Patel et al explored this issue anew by removing from the analysis those preterm deliveries that they considered were not due to HIV therapy. The overall rate of transmission in their population was 16.7 percent and a significant association between PI-based HAART and severe PTD (<32 weeks) compared with non-PI-based HAART, which was mostly triple nucleoside analog RT inhibitor therapy, was found (2% v 0%, $P = 0.04$). Whether the exclusion of women with pre-eclampsia from the analysis is justified, given the several publications that have found a lower than expected rate of pre-eclampsia in untreated HIV infected women with restoration of risk attributable to HAART,[99-101] is a moot point.

To summarize the data thus far: Most European studies and some others find an association between HAART and PTD whilst there is a general perception that N. American studies present conflicting data. Despite this, three studies from N. America—the PSD, Cotter's study from the Miami cohort[102] and Patel's study, all report an association between PI-based HAART and some

degree of PTD. Important questions therefore remain: Is there confounding bias?—If so, this is likely to become less as general treatment guidelines move to earlier therapy. Does the timing of HAART matter? If HAART prior to conception is a risk for PTD then the problem will not go away. If HAART during pregnancy is the risk than earlier treatment and more universal treatment will be beneficial. Is any HAART a problem or is it really only PI-based HAART and if the latter, does it matter which PI? Our own data suggest PI-based HAART has a bigger effect than NNRTI-based HAART but both are associated with more PTD than ZDVm. Do individual drugs matter? To date the only non-PI based HAART combination has been nevirapine based (if triple nucleoside combinations are excluded). This is likely to change as new members of this and other classes gradually become more commonly used during pregnancy. Understanding the reasons for the different reported outcomes is likely to help unravel the conundrum. The different results will not be because one is right and another wrong but to a multitude of local or regional factors including differences in the populations. Finally and most importantly, we have to ask does it matter? In resources-rich settings, mild PTD will have limited impact on survival. However, in some studies the reported effect has been most marked with severe PTD. In the ECS the mortality among infants born prior to week 34 was 7.4 percent. This effect is likely to be even in resource-limited settings. For this reason alone, this question must be resolved to allow the safest possible use of antiretroviral therapy, which is the pillar on which PMTCT currently stands. In the Mma Bana study, comparing a triple NRTI regimen with PI-based HAART for PMTCT during pregnancy and 6-months exclusive breastfeeding, PTD was observed in 23 percent of the women randomized, at 26-34 weeks, to the PI-arm, in 15 percent of the women randomized to the NRTI only arm and in only 10 percent of the women in the observational arm who, having CD4 cell counts less than 200/µl, commenced nevirapine-based HAART at 18-34 weeks as per standard of care in Botswana.[103]

An association between PI-based HAART and diabetes has been reported including several specifically relating to pregnancy, although there is disagreement over whether this is with early[104] or late[105] therapy. However, this has not been a universal finding[106,107] and in a prospective multicenter study no evidence of increased glucose intolerance or insulin resistance was found in women taking protease inhibitors compared with those non-PI-based therapy.[108]

The Effect of Antiretroviral Therapy on PMTCT Risk other than HIV Viral Load

With the suppression of HIV replication to levels below the limit of detection of most current assays, especially when this is occurring well prior to the time of delivery and with the knowledge that transmission rates in women taking HAART are now 1 percent or below, it is not surprising to find that the list of risk factors for MTCT is, in this setting, shrinking. However, it is important to make this point, since confidence in the effective management of pregnant women will allow a more natural child-birth experience. In the UK, whilst there has been a shift away from PLCS to intended normal spontaneous vaginal delivery, this has not led to much shift towards actual vaginal deliveries. The observed effect is for a reduction in PLCS and an increase in emergency CS with the impression being that the threshold for the latter is much lower for HIV infected women, despite fully suppressed viral replication, than for the general population.

Even treatment with ZDVm influences the importance of the various risk factors. Thus in the Perinatal HIV Prevention Trial –1, where HIV positive mother-infant pairs in Thailand were randomized to short or long courses of ZDVm, only a limited number of risk factors for transmission could be identified. *In utero* transmission was associated with maternal viral loads >35,000 HIV RNA copies/ml plasma, with delayed start of ZDVm prophylaxis until after 31.4 weeks. Intrapartum transmission was associated with viral loads >10,000 HIV RNA copies/ml plasma, with induction of labor and with tocolysis for PTD. PTD remained a risk factor for transmission when both groups were combined, along with low birth weight (<2500 g) and with increased maternal serum creatinine.[109] Scavalli et al have shown how the risk of transmission associated with being the first-born twin has fallen during the HAART era (1997–2003) from 28.3 percent pre-1996 to 1 percent.[110] The risk of transmission associated with acute chorioamnionitis appears to be abrogated by sdNVP. As one would expect sdNVP had no effect on transmissions associated with chronic chorioamnionitis.[111]

Development of Resistance to Antiretroviral Therapy during PMTCT

Successful therapy must combine both antiviral efficacy, in terms of the drug(s) ability to inhibit viral replication, and a high barrier to resistance. Barriers to resistance vary widely between individual compounds and the current HAART strategy has been based on combining therapies to prevent the emergence of drug resistant strains. With better understanding of treatment failure, the concept of the barrier in terms of the number of mutations necessary to blunt anti-viral efficacy rather than the number of compounds in the combination has emerged leading to studies which once again look to explore the possibility of monotherapy, e.g. with darunavir. To date, noninferiority during long-term follow-up has not been proven but simplification of therapy remains a therapeutic goal.

Whilst ZDV has been the keystone of ART in PMTCT the development of resistance during ZDVm, which may dull the impact of therapy, results in transmitted resistance and impact on future maternal therapeutic choice and outcome is a legitimate concern. In ACTG 076, mutations in HIV *pol* associated with reduced zidovudine sensitivity were noted in a minority of patients. Treatment with ZDVm was started from the 14th week of gestation and continued to delivery with a median of 11 weeks on ZDVm, maternal CD4 counts were all >200 cells/ml and only 4 percent of participants had prior antiretroviral therapy exposure. In a sub-study, there was some evidence of new ZDV resistance associated mutations emerging during therapy, with the prevalence of low-level ZDV resistance at baseline being (95% CI) 0.3-6.8 percent and the incidence at delivery 0.3-14 percent. No high level resistance emerged during the study. Only two codons were examined: K70R and T215F/Y. Viral load, rather than resistance, was associated with transmission.[112] In the WITS cohort, the presence of at least one ZDV mutation was associated with an increased rate of transmission (OR 5.15, 95% CI 1.4-18.9)[113] whereas although Palumbo et al found ZDV mutations in 17 percent of pregnant women on ZDV in a prospective study, only 2/24 infected infants had ZDV mutations and these differed from the maternal pattern. They therefore concluded that an association between ZDV mutations and transmission was not demonstrated.[114] Can ZDV mutations be avoided in PMTCT? Shorter courses may avoid this as were used in Cote d'Ivoire.[115] Selection of recipients with longer risk of developing resistance is also possible. Thus since 2004, British HIV Association guidelines have restricted ZDVm use to healthy pregnant women with CD4 counts >200 cells/ml, HIV viral loads <10,000 cpm who start ZDVm at 28 weeks and deliver by PLCS at 38-39 weeks.[116] Studies of women treated according to these guidelines have shown no evidence of ZDV mutations emerging during treatment, neither in the consensus sequence[117] nor in clonal analysis.[118] None of 470 women treated, according to these guidelines have transmitted HIV.[71]

The situation with lamivudine is different. A single point mutation at codon M184 reducing sensitivity 100-fold. Despite, being used in combination with zidovudine and demonstrating efficacy in reducing viral load and MTCT, the M184V develops rapidly and frequently.[58,119,120]

Perhaps the most contentious issue relates to the use of sd NVP to mother and infant. The efficacy in PMTCT has been documented above. At the time of the first reports of HIVNET 012, there were no data on NVP resistance with this approach, rather anecdotal reports of rapid treatment failures. Like lamivudine, NVP is highly effective in reducing viral load but has a low barrier to resistance. Gradually the evidence of NVP resistance following even a single dose of nevirapine given in labor emerged.[121] This can be attributed not only to the efficacy of the therapy but also to its long half-life, the very features, along with rapid absorption and transplacental transfer, that made it so attractive an intervention. The earlier after treatment that mutations are sought and the more intensive the investigation, the more commonly they are found. There is also some evidence of clade effect, with resistance more common with clade D than A[122] whilst HIV-1 clade C may be most susceptible with resistance found in up to 77 percent of mothers tested 2 weeks post-dose.[123] There is also evidence of rapid waning of the mutation among circulating virions.[124] The next question is does it matter? Subsequent use of NNRTI-based HAART certainly performs less well in women known to have had detectable genotypic nevirapine resistance than women never exposed, with nevirapine - exposed women, no mutation detected, having an intermediate response.[125] The development of NVP resistance mutations can be reduced by adding zidovudine and lamivudine to the maternal regimen for a short period,[126] yet to be completely optimized. There may be some cost in terms of a small risk of lamivudine resistance with this approach. If HAART is available then it makes sense to avoid nevirapine for PMTCT. If HAART is not available, then a combination of short-course ZDVm plus IP NVP plus zidovudine/lamivudine to cover the NVP tail, is both effective to PMTCT and reduces the risk of resistance. The most significant impact of sdNVP on future treatment responses is in the first few months with a reduced effect if initiation of HAART is deferred beyond 12 months.

Whilst resistance can occur to any failing ART regimen, there is no evidence to suggest that failure during HAART is more common in pregnancy and indeed there is evidence of high success rates.[127] The pharmacokinetics of ARVs are, in some cases, altered during pregnancy as discussed elsewhere, but with perhaps the exception of nelfinavir, this has not been of clinical significance.

Conclusion

In the context of a comprehensive PMTCT program built on universal recommendation for antenatal HIV testing and post-test support, antiretroviral therapy is essential to reduce the risk of HIV infection *in utero* and intrapartum. Whilst mother-infant sdNVP reduces transmission by 40 percent, this should be seen as a stop-gap measure pending the rollout of more effective interventions. 3rd trimester ZDVm supplemented with sdNVP and a short course of HAART to reduce the risk of NVP resistance in the mother can reduce pre- and perinatal transmission to 1-2 percent. HAART, which is now recommended for all adults with a

CD4 count less than 350 cells/μl, if initiated early enough in pregnancy, reduces transmission to <1 percent and the recent analysis by Khun et al indicates that 88 percent of all transmissions and 92 percent of maternal deaths would be prevented by applying these new criteria for starting therapy.[128] Problems related to HAART, especially PTD, cannot be ignored and every effort should be made to refine HAART in pregnancy to ensure that it is as safe and effective as possible. Not withstanding this, the benefits of current HAART far outweigh the known risk for mother and baby and universal access to HAART during pregnancy has the potential to restrict HIV MTCT to rare events.

Case Studies

Case 1

A 25-year-old, gravida 2, parity 1, presents to the labor ward in early labor on a Saturday evening having received no antenatal care. She has been well throughout the pregnancy and is now 39 weeks gestation. Her first born died age 3 months of failure to thrive and pneumonia. Examination is normal for a term pregnancy except that she has mild pallor and white plaques on the lateral tongue margins and buccal mucosa. She consents to a HIV Ab test but the routine laboratory is closed and the result will not be available until Monday afternoon.

Do you:

A. Recommend an Emergency cesarean section.
B. Commence IV zidovudine.
C. Prescribe a dose of Nevirapine 200 mg stat.
D. Start HAART.
E. Wait for the HIV antibody test result.

Answer C

A randomized controlled clinical trial has shown this to be an effective method to reduce HIV MTCT in established labor. Adding IV zidovudine at this stage has minimal benefit and there is often a delay preparing the infusion. Nevirapine is rapidly absorbed and crosses the placenta efficiently with adequate fetal plasma concentrations achieved within 2 hours. Emergency sections in established labor offer less protection than a PLCS and the lack of antenatal care during this pregnancy suggests that this would place her at additional obstetric risk in any subsequent pregnancy. Given the clinical picture of oral hairy leucoplakia, it is likely that this patient will require HAART but this should only be started after appropriate education and discussion and more thorough assessment. Trimethoprim-sulphamethoxazole to prevent PCP and cerebral toxoplasmosis is a reasonable option pending a CD4 count. Waiting for the HIV antibody test is not an option, as the window of opportunity will have passed.

Case 2

A 20-year-old female presents to your clinic for review. She has history of Pneumocystis jirovecii pneumonia two years ago following which she was treated with a fixed dose combination of tenofovir, emtricitabine and efavirenz. She has tolerated this well and her CD4 count is now greater than 200 CD4+ lymphocytes/ml. She complains that she hasn't had a period for 2 months. A urine pregnancy test is positive.

Do you:

A. Stop all antiretroviral therapy as these are not licensed in pregnancy.
B. Stop all antiretroviral therapy until the second trimester and then start zidovudine.
C. Stop all antiretroviral therapy until the second trimester and then start nevirapine plus fixed dose zidovudine/lamivudine.
D. Switch therapy immediately to ritonavir-boosted lopinavir, tenofovir and fixed dose emtricitabine.
E. Continue fixed dose combination of tenofovir, emtricitabine and efavirenz.

Answer E

Despite the recommendation that efavirenz is not prescribed to women who may become pregnant, this is mostly ignored and conception whilst taking efavirenz is a common scenario and advise on what to do differs between guidelines. Although it is correct that, with the exception of zidovudine, antiretroviral therapy has not been licensed for use in pregnancy, all HIV management guidelines recommend the use of antiretroviral therapy where indicated for maternal health, including during the first trimester. HAART after the 2nd trimester is also recommended for HIV PMTCT. This patient is at risk of opportunistic infections if her therapy is discontinued. Whilst some guidelines recommend switching from efavirenz, the history, which could be confirmed by ultrasound examination suggests that the fetus is 42 days old. If this is the case, the neural tube will already have closed and any risk of myelomeningocele attributable to efavirenz exposure has already occurred. Many clinicians would therefore choose to continue her present, well tolerated and effective treatment. Some would however switch even at this late stage to an alternative as in answer D, mostly for medico-legal reasons. In the latest interim report from the Antiretroviral Pregnancy Registry (data to end January 2010) 546 first trimester exposures to efavirenz had been reported with 14 (2.6%) congenital malformations, including a single case of myelomeningocele. The reported incidence of myelomeningocele in live and stillbirths in the general population of Europe in 2000 was a little under 1 per 1000. Although these data are encouraging, as yet, there have been insufficient reports to exclude an increased risk of myelomeningocele following efavirenz exposure

and prospective reporting of all antiretroviral exposure during pregnancy to the APR is highly important (*www.apregistry.com*).

Key Messages

- Zidovudine monotherapy and intrapartum nevirapine reduce MTCT by prophylaxis in the newborn
- Peripartum HIV MTCT risk can be as low as 1:1000 for mothers on HAART with a viral load of <50 HIV RNA copies/ml plasma at delivery
- With no treatment or ZDVm pre-labor cesarian section (PLCS) reduces MTCT by up to 80 percent but PLCS is not indicated for mothers on effective HAART.

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3.4

Care of a Child Born to a HIV Positive Mother

Radhika Singh

Introduction

HIV infection is a chronic illness and clinical manifestations vary depending on the rate of progression of the disease. Some children are rapid progressors with rapid progression of the disease in the first 2 years of life leading to mortality in 50 percent by 2 years of age and 75 percent by 5 years of age, and children who are late progressors have repeated episodes of pneumonia (persistent and recurrent), diarrheal diseases, cryptococcal meninigitis, etc with increase in morbidity. Routine care of a HIV infected child requires a multidisciplinary approach from pediatricians, social workers, dentists, psychologists, etc. Care of the mother should also be integrated into the care of the child.

Natural Course of HIV Infection in Infants

One needs to understand the distinction between HIV exposed and HIV infected neonate. Exposed neonates can be infected with HIV in three ways, viz antepartum, intrapartum and postpartum.

Vertical transmission of HIV can occur:
- *In utero*
- During labor
- After delivery

5-20 percent of infants become infected through breastfeeding. In breastfeeding populations 25-40 percent of infants born to HIV infected mothers will acquire HIV disease without intervention.

It is estimated that in 65 percent of HIV infected infants, transmission occurred during labor. Multiple factors increase the risk of vertical transmission of HIV (Table 3.4.1).

Table 3.4.1: Factors increasing the risk of vertical transmission of HIV

Maternal factors	*Intrapartum events*
• Low CD4+ lymphocyte count	• Instrumental delivery
• High viral load	• Use of fetal scalp monitor
• Advanced AIDS	• Fetal scalp pH measurement
• Preterm delivery	• Use of DeLee suctioning
• Chorioamnionitis	• Artificial rupture of membranes
• Presence of p24 core antigen	• Rupture of membranes for longer than 4 hours
	• Other events increasing fetal exposure to maternal blood

HIV = Human immunodeficiency virus; AIDS = Acquired immunodeficiency syndrome.

Information from Public Health Service Task Force recommendations for the use of antiretroviral drugs in pregnant HIV-1 infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States. Living document: January 24, 2001. Retrieved February 2001, from http://www.hivatis.org/trlgdlns.html#Perinatal.

HIV infection in infants appears to have two forms. The first form, which is similar to HIV infection in adults has a prolonged course, with HIV infection progressing to AIDS over 8 to 10 years. The second and more aggressive form is characterized by early conversion to AIDS and an increased risk of opportunistic infections and mortality.

Early HIV infection increases the risk of rapid progression to AIDS. Defined as a positive virologic test fewer than 48 hours after delivery, early infection is the result of *in utero* HIV transmission, as opposed to intrapartum or postpartum transmission. In a French study of HIV infection in children, newborns with hepatosplenomegaly, lymphadenopathy, fewer than 30 percent CD4+ lymphocytes or a positive HIV DNA polymerase chain reaction (PCR) test within the first week

after birth were found to be at increased risk for rapid progression of HIV infection. A retrospective study from the intravenous immunoglobulin prophylaxis clinical trial found that increased viral loads and decreased CD4+ lymphocyte counts increased the relative risk of mortality in HIV infected infants.

Care of the infant begins way before the infant's birth, whereby the mother is given antiretroviral medication to prevent transmission of HIV to the fetus. This can be done in the intrapartum and the antepartum period. Apart from antiretrovirals, various other measure are taken to prevent transmission.

The pediatrician plays a key role in prevention of MTCT(mother-to-child transmission) of HIV-1:

- Identifying HIV-1 exposed infants even if the mother's HIV-1 infection was not recognized before delivery
- Prescribing ARV prophylaxis for infants born to HIV-1 infected women to reduce the risk of MTCT
- Further reducing the risk of HIV-1 transmission by advising women on feeding choices.

In addition to standard pediatric care, the pediatrician is also responsible for:

- monitoring of the infant for early determination of HIV-1 infection status
- evaluation for possible short- and long-term toxicities of *in utero* and neonatal ARV exposure
- providing chemoprophylaxis for *Pneumocystis jirovecii* pneumonia (PCP) as required
- administering vaccines as appropriate
- supporting families living with HIV-1 infection, including providing counseling to parents or caregivers.

Care of the infant or child with perinatal infection with HIV-1 should be undertaken in consultation with a pediatric HIV specialist.

When a Neonate is Born to a HIV Positive Mother the Following Steps are Taken

1. Adequate Maternal History to Evaluate Maternal Co-infection

At the time of the initial assessment of the infant, maternal health information should be reviewed to determine if the infant has been exposed to maternal coinfections, including tuberculosis (TB), syphilis, toxoplasmosis, hepatitis B or C, cytomegalovirus, or herpes simplex virus. Although there is little information as to the relative transmission or infection rates of such pathogens in infants of mothers with HIV-1 infection, there is concern that reactivation of latent infections in immunocompromised pregnant women may cause increased risk of transmission to, and disease in, exposed newborn infants. Diagnostic testing and treatment of such coinfections in infants born to women with HIV-1 infection are based both on maternal findings and evaluation of the infant. In the absence of suggestive history or routine evaluation, specific laboratory testing for these pathogens is not recommended.

If the mother is on anti-tuberculous therapy information regarding duration of therapy should be obtained. If there is history of tuberculosis in the mother the following investigations are undertaken in the neonate which includes:

a. Gastric washings X 3.
b. Chest X-ray.
c. Liver function tests.
d. Cerebrospinal fluid analysis for AFB (acid-fast bacilli).

If gastric washing and or/CSF is positive the child should be started on a full course of Anti-TB treatment.

Once a pregnant women has been on treatment for at least 2-3 weeks, she is generally no longer infectious. The risk is highest to the neonates if the mother is diagnosed at the time of delivery or shortly after. In this case the baby and placenta should be investigated for evidence of congenital TB infection and treated. A breastfeeding infant has a high-risk of infection from a mother with smear-positive pulmonary tuberculosis and has a high-risk of developing TB. The infant should receive 6 months of INH preventive therapy, followed by BCG vaccination. If a mother has MDR-TB the neonate still receives INH prophylaxis and these infants should be followed for a period of two years. WHO does not recommend second line drugs for chemoprophylaxis in MDR-TB contacts.

Other history from the mother includes history of syphilis, CMV, toxoplasmosis or gonorrhea.

2. Feeding Choice

Mother is counseled extensively regarding feeding choice during the antenatal period. In developed countries, one of the absolute contraindications for breastfeeding is HIV in the mother. In developing countries, the risk of diarrheal disease is high due to lack of safe drinking water. Formula feeds can be a problem due to unsafe washing of bottles, thus increasing the risk of diarrheal diseases and hence the risk of transmission of HIV. Many studies have shown that exclusive breastfeeding compared to mixed feeding by mothers for the first six months decreases the risk of transmission. The mother is counseled regarding choice of feeding which includes:

a. **Exclusive breastfeeding:** For the first six months of life, which means no water or any other feed during the first six months. If the mother decides to stop breastfeeding, ARV prophylaxis should be continued for one week after breastfeeding is stopped.

When a mother decides to stop breastfeeding, the infant should be provided with safe and adequate replacement (Table 3.4.2) feeds. Mothers who choose

Revised WHO Recommendations on the use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants (2009) (http://www.who.int/hiv/topids/mtct/)

For all HIV-infected pregnant women who are not eligible for ART, ARV prophylaxis for preventing HIV transmission through breast milk (option A consists of daily nevirapine to the infant; option B consists of triple ARV drugs provided to the pregnant women starting from as early as 14 weeks of gestation) should continue until one week after all exposure to breast milk has ended.

exclusive breastfeeding, are encouraged to flash heat or heat treat the breast milk. Many studies have shown that flash heating of breast milk inactivates the virus and decrease the risk of transmission through breast milk.

Flash heating technique: A minimum of 50-100 ml of breast milk is placed in a 1-quart pan filled with 450 ml of water. The water and milk are heated together over a single-burner butane stove. Once the water reaches a rolling boil, the breast milk is immediately removed and allowed to cool. This method protects the anti-infective and nutritional properties of breast milk.

Advantages of breastfeeding include

- Protective maternal antibodies
- Does not depend on the availability of clean water
- Does not impact maternal health status.

Disadvantages of breastfeeding include

- Risk of HIV transmission especially if the mother has subclinical mastitis or fungal infection of the nipple/areola.

b. **Exclusive formula feed:** Mother is advised for formula feeds if she meets the AFASS criteria which includes:
   i. **Acceptable:** The mother perceives no problem in replacement feeding. Potential problem may be cultural, social, or due to fear of stigma and discrimination.
   ii. **Feasible:** The mother (or family) has adequate time, knowledge, skills, resources and support to correctly mix formula or milk and feed the infant up to 12 times in 24 hours.
   iii. **Affordable:** The mother and family, with community or health system support if necessary, can pay the cost of replacement feeding without harming the health or nutrition status of the family.
   iv. **Sustainable:** Availability of a continuous supply of all ingredients needed for safe replacement feeding for up to one year of age or longer.
   v. **Safe:** Replacement foods are correctly and hygienically prepared and stored, and fed preferably by cup.

Source: IMCI Complementary Course on HIV/AIDS; Module 3; Counselling the HIV Positive *Mother. WHO 2007.*

If the mother meets the AFASS criteria she can be encouraged to formula feed.

Advantages of Formula Feeding

- Decreased risk of PMTCT
- Does not depend on mothers health

Disadvantages of Formula Feeding

- Costly and not readily available
- No maternal antibodies
- Needs clean water and clean supplies
- Need supplies on hand when not at home.

Table 3.4.2: The other history to be taken to make an informed decision includes

Question	*Breastfeeding*	*Replacement feeding*
Where do you get your drinking water?	River, stream, pond, or well	Piped water at home or can buy clean water
What kind of latrine/toilet do you have?	None or pit latrine	Waterborne latrine or flush toilet
How much money could you afford for formula each month? Ps: calculate the amount-based on the local costs	Less than minimum required amount available for formula each month	Minimum amount required for formula every month
Do you have a refrigerator with reliable power?	No, or irregular power supply	Yes
Can you prepare each feed with boiled water and clean utensils?	No	Yes
How would you arrange night feeds?	Preparation of milk feeds at night difficult	Preparation of milk feeds at night possible
Does your family know that you are HIV positive?	No	Yes
Is your family supportive of milk feeding and are they willing to help?	Family not supportive and not willing to help, or do not know–can not discuss	Family supportive and willing to help

Source: Mother and child nutrition

If the mother does not meet the AFASS criteria she is encouraged to exclusively breastfeed for the first six months.

To enable mothers to establish and sustain exclusive breastfeeding for 6 months, WHO and UNICEF recommend:

- Initiation of breastfeeding within the first hour of life
- Exclusive breastfeeding—the infant only receives breast milk without any additional food or drink, not even water
- Breastfeeding on demand – that is as often as the child wants, day and night
- No use of bottles, teats or pacifiers.

c. **Mixed feed:** Mothers who are HIV positive must be discouraged from mixed feeding (formula+breast) since this enhances HIV transmission.

3. Antiretroviral Perinatal Transmission Prophylaxis

Apart from maternal antiretroviral therapy, antiretrovirals are initiated in the neonate within 72 hours after birth. Various regimes are followed in different countries for prophylaxis. In South Africa the regime is Nevirapine (NVP) to the neonate for the first six weeks of life. If the mother has chosen formula feeds, NVP can be stopped after 6 weeks and if she has chosen breastfeeds NVP can be continued in the infant as long as she breastfeeds.

Revised WHO Recommendations on the use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants (2009).

The 2009 recommendations provide two alternative options for women who are not on ART and breastfeed in resource-limited settings:

- If a woman received AZT during pregnancy, daily nevirapine is recommended for her child from birth until the end of the breastfeeding period

OR

- If a woman received a three-drug regimen during pregnancy, a continued regimen of triple therapy is recommended through the end of the breastfeeding period

4. Monitoring for Toxicity from in Utero and Neonatal ARV Drug Exposure and Monitoring for and management of short-term toxicity during infant ARV prophylaxis

A baseline hemoglobin or complete blood cell and differential count should be performed on the newborn infant, because infants whose mothers have received ARV agents during pregnancy are at risk of small but measurable differences in several hematologic variables, including hemoglobin level and neutrophil and lymphocyte counts. The risk of anemia and neutropenia is greater in infants whose mothers were treated with combination ARV therapy during pregnancy, but anemia is also more common in infants whose mothers were treated only with ZDV compared with infants whose mothers received no ARV treatment during pregnancy. Nevertheless, the benefits of maternal ARV therapy in prevention of MTCT of HIV-1 clearly outweigh the risks of this hematologic toxicity in the newborn infant.

Anemia is the primary clinically important complication of the 6 weeks ZDV regimen in the neonate, but it is unusual for the anemia to be clinically significant. Anemia associated with ZDV prophylaxis resolves when ZDV is stopped. Severe anemia that persists after prophylaxis is stopped should be further evaluated for alternative etiologies. Hematologic toxicity is more significant in infants who were exposed to antepartum ZDV in combination with other ARV drugs and in infants who received both ZDV and lamivudine as infant prophylaxis for 6 weeks. Although anemia is mild and asymptomatic in most term infants treated with ZDV, it may be more severe in preterm infants or those with additional medical problems.

Decisions about the timing of hematologic monitoring of infants treated with prophylactic ARV agents after birth depend on a number of factors, including baseline hematologic values, gestational age at birth, clinical condition of the child, receipt of concomitant medications, and maternal antepartum therapy. Some experts recheck hematologic values in a healthy infant who is receiving 6 weeks of ZDV prophylaxis only if the child is symptomatic, and others recheck hemoglobin and/or neutrophil counts after 4 weeks of ZDV treatment, particularly if the infant was born preterm or if trimethoprim/sulfamethoxazole prophylaxis is anticipated.

If hematologic abnormalities are identified, decisions on whether to continue infant ARV prophylaxis need to be individualized. Considerations include the extent of the laboratory abnormality, associated clinical symptoms, duration of infant prophylaxis already received, the magnitude of the risk of HIV-1 infection in the infant (as assessed by maternal receipt of ARV prophylaxis, maternal viral load near delivery, and mode of delivery), and availability of alternative interventions (e.g. erythropoietin, red blood cell transfusion). Consultation with a pediatric HIV-1 specialist is advised if early discontinuation of prophylaxis is considered.

5. Counseling of Parents

The parents should be informed that it may take many months before the child be determined to be infected or uninfected. The mother should be counseled regarding immunization of the infant and *Pneumocystis jerovecii pneumonia* prophylaxis (PCP/PJP).

6. Immunizations

Routine immunizations should be given to all HIV exposed children according to the schedule. HIV exposed children should not receive live virus or live bacterial vaccines, with the exception of measles-mumps-rubella vaccine and varicella vaccine. The inactivate polio vaccine should be given instead of the live oral vaccine. Though BCG is a live attenuated vaccine, it is administered to neonates at birth in developing countries since Tuberculosis is highly prevalent in developing countries. So the benefits of giving BCG outweighs the risk. One of the complications of BCG vaccine in HIV exposed children is BCGiosis or disseminated TB.

WHO recommendations for BCG vaccination is as follows:

The HIV pandemic has implications for BCG vaccination. Although there have been a few reports of disseminated BCG disease after BCG immunization of HIV infected children, prospective studies comparing BCG immunization in HIV infected and uninfected infants have showed no difference in risk of complications. It is recommended that BCG vaccination policy should depend on the prevalence of TB in a country. In countries with a high TB prevalence, the benefits of BCG vaccination outweigh the risks, and WHO recommends a policy of routine BCG immunization for all neonates. A Child who has not had routine neonatal BCG immunization and has symptoms of HIV disease/acquired immunodeficiency syndrome should not be given BCG because of the risk of disseminated BCG disase. BCG should not be given to HIV infected children in low TB prevalence countries.

Recommended Vaccines

- Diphtheria
- Tetanus
- Pertussis
- Polio (only inactivated polio)
- Hemophilus influenzae type B (HIB)
- Pneumococcus
- Meningococcus
- Mumps
- Rubella
- Rotavirus.

Vaccines to Avoid

- *BCG:* It can cause TB infection in people with immune systems weakened by HIV
- *Polio:* The live virus polio vaccine should not be given to HIV infected kids because it can cause disease. Inactivated polio vaccine is recommended for children with HIV.

Live attenuated vaccines

Rotavirus vaccine

- No safety efficacy data are avaliable for the administration of attenuated rotavirus vaccine to infants who are potentially immunocompromised, including those who are HIV-positive. As HIV diagnosis may not be established in infants born to HIV positive mothers before the age of the first rotavirus vaccine dose, and only 1.5-3% of HIV-exposed infants in the US will eventually test HIV positive, guidelines support vaccination of HIV exposed or infected infants.
- Schedule: Rotateq, 2,4, and 6 months; rotarix, 2 and 4 months. First dose should be administered at age 6-14 weeks. Final dose should not be administered later than age 32 weeks.

Varicella vaccine

- Single antigen varicella (VZA) primary vaccination may be considered in HIV infected, VZV-seronegative persons aged >8 years with CD4 cell counts >200 cells/mm and HIV-infected children aged 1-8 years with CD4 cell percentages ≥15%.
- Limited data are available on safety and immunogenicity of VZV vaccine in HIV infected children, however, weighing the risk for severe disease from wild VZV and the potential benefit of vaccination, experts agree to consider vaccination unless severely immunocompromised (CD4 <15%).
- Schedule: Two doses 3 months apart; first dose at 12 months
- combined MMR and varicella vaccine (MMRV) has not be substituted for single antigen varicella vaccine
- Immunogenicity might be lower in HIV infected adolescents (and adults)

Measles, Mumps and Rubella vaccine (MMR)

- MMR vaccine is recommended for HIV infected children who are not severely immunosuppressed (CD4+ ≥15%) and who lack evidence of measles immunity
- The first dose of MMR vaccine should be administered as soon as possible afer the first birthday. Consider administering the second dose 1 month after the first dose rather waiting until age 4 to 6 years.
- MMRV vaccine has not been studied in HIV infected children and should not be substituted for MMR vaccine.

Inactivated vaccines

Hepatitis B vaccine (HepB)

Hepatitis B vaccination follow routine immunization recommendatons with the following:

- *Postvaccination:* Testing is recommended for HIV infected children, 1-2 months after administration of the last dose of the vaccine series to verify achievement of a protective level of anti-HBs levels of <10 mIV/mL followed by anti-HBs testing 1-2 months after the 3rd dose.
- *Booster dose:* In HIV infected children, the need for booster doses has not been determined. Annual anti-HBs testing with booster doses when anti-HBs levels decline to <10 mIU/mL should be considered in persons with ongoing risk of exposure.
- Modified dosing regimens, including a doubling of the standard antigen dose might increase response rates.

Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP), (Tdap), and Hemophilus influenzae type b conjugate vaccine (Hib).

- Recommendations in HIV infected patients mimic routine immunization schedule.
- Clinicians might consider use of Hib vaccine in HIV infected >59 months who did not receive the vaccine.

Pneumococcal vaccine
- Heptavalent pneumococcal conjugate vaccine (PCV) is re-commended for all HIV infected children aged 2-59 months, Children ≤23 months should be vaccinated according to the routine PCV schedule
- For incompletely vaccinated children aged 24-59 months, administer 2 doses of PCV at least 8 weeks apart
- Administering PCV to HIV-infected children ≥5 years is not contraindicated. Many experts would consider administering PCV vaccine followed by 23-valent pneumococcal polysaccharide (PPV) in this age group if previosly not vaccinated
- Children aged ≥2 years should also receive the 23-valent pneumococcal polysaccharide vaccine (PPV) ≥2 months after their last PCV dose with a single revaccination with the 23-valent vaccine 3-5 years later
- A 13-valent pneumococcal conjugate vaccine is under study

Influenza vaccine
- All HIV infected children (aged 6 months and older) and adolescents, and close contacts (including household members) of these children are recommended to receive yearly trivalent inactivated influenza vaccine (TIV)
- For healthy close contacts aged 2-49 years, live, attenuated influenza vaccine (LAIV) may be used as an alternative to TIV
- Vaccination schedule and doses are similar to those recom-mended for healthy children and adolescents
- Administration of H1N1 influenza vaccine in addition to the routine seasonal influenza vaccine will likely be recommended in 2009

Hepatitis A vaccine
- Hepatitis A vaccine is recommended for all children aged 1 year
- Schema: 2 doses, 6 months apart
- Review hepatitis A status in HIV patients, in particular in patients at higher risk, including MSM, IVDU, GI disease, clotting disorders, and co-infected with hepatitis B or C

Meningococcal vaccine
- Children with HIV are at increased risk for meningococcal disease although not to the extent that they are at risk for invasive *Streptococcus pneumoniae* infection
- Although the efficacy of MCV4 among HIV infected children is under study, this vaccine is recommended in HIV infected children at ≥ 2 years
- Revaccination with MCV is indicated for children through age 18 years who received MCV4 or MPSV at ages 2 through 6 years or after 6 years, at 3 or 5 years after their first dose, respectively

Human papillomavirus vaccine (HPV)
- No data are available on immunogenicity, safety and efficacy of HPV vaccine in HIV infected females but clinical trials are ongoing
- Because quadrivalent HPV vaccine is a noninfectious vaccine, and HPV related disease is increased in HIV positive patients it can be administered to females regardless of CD4%
- Schema: females at age 11-12 years at 0, 2 and 6 months (minimum age 9, maximum age 26 years)

Inactivated poliovirus vaccine (IPV)

Recommendations in HIV infected patients mimic routine immunization schedule. Oral polio vaccine is contraindicated in HIV infected children and adolescents

Source: Update of immunizations in HIV infected and exposed children and adolescents—division of infectious diseases—University of South Florida.

- *Chickenpox:* Because the chickenpox vaccine is a live vaccine, it can cause a disseminated chickenpox infection in those kids with weakened immune systems. Avoiding all live vaccines is usually what is recommended, although some will give HIV positive children the chickenpox vaccine if their immune system is strong and healthy. Please refer to the chapter on "Immunizations for the HIV Infected Child" for more details.

7. Pneumocystis Carinii Pneumonia (PCP) Prophylaxis in HIV Exposed and Infected Children

Antimicrobial prophylaxis is very effective in preventing PCP. Cotrimoxazole prophylaxis is safe, inexpensive and highly effective in reducing morbidity and mortality among HIV infected infants and children. WHO recommends that all HIV exposed infants be started on co-trimoxazole prophylaxis at 4 to 6 weeks of age, in order to provide adequate prevention against early opportunistic infections. This is particularly critical for HIV-infected infants.

All patients born to HIV infected mothers should receive PCP/PJP (Pneumocystis jerovecii pneumonia) prophylaxis, with such prophylaxis being discontinued once HIV infection has been definitively excluded. TMP-SMZ (Trimethoprim-sulphamethoxazole) is also effective in preventing toxoplasmosis. Peak incidence of PCP infection is 3-6 months and the case fatality rate is 40-90%.

WHO recommendations for PCP prophylaxis include the following:

Initiating PCP Prophylaxis Among HIV-exposed Infants

All infants born to HIV infected women should be started on PCP prophylaxis at 4-6 weeks of age, regardless of their CD4+ count (Table 3.4.3). Infants who are first identified as being HIV-exposed after 6 weeks of age should be started on prophylaxis at the time of identification. These recommendations are based on the following considerations:

- Most cases of PCP among HIV infected children occur in the first-year of life
- The risk for PCP begins to increase dramatically at age 2 months (when HIV infection cannot yet be reasonably excluded)
- The reliability of CD4+ counts in predicting which infants are at risk for PCP is relatively low during infancy particularly among infants less than or equal to 6 months of age, the age at which the peak incidence of PCP occurs.

PCP prophylaxis should not be administered to infants less than 4 weeks of age because

- They are at low risk for PCP
- The use of sulfa drugs among infants at this age is not advised because of the potential for adverse drug effects resulting from immature bilirubin metabolism. Additionally, the concurrent use of sulfa drugs among HIV-exposed infants who are receiving zidovudine during the first 6 weeks of

life to prevent perinatal HIV transmission could potentially exacerbate the anemia that some children receiving zidovudine experience.

Therefore, to avoid the potential for additional toxicity in such children, prophylaxis should be started at 6 weeks of age, the age at which zidovudine is discontinued.

PCP Prophylaxis for Infants 4-12 Months of Age

- All HIV infected infants and infants whose infection status has not yet been determined should continue prophylaxis until 12 months of age.
- PCP prophylaxis should be discontinued among infants in whom HIV infection has been reasonably excluded on the basis of two or more negative viral diagnostic tests (i.e. HIV culture or PCR), both of which are performed at greater than or equal to 1 month of age and one of which is performed at greater than or equal to 4 months of age. For children who do not have access to such testing, prophylaxis should be continued until 12 months of age unless HIV infection has been excluded on the basis of two or more negative HIV- antibody tests performed at greater than or equal to 6 months of age.

PCP Prophylaxis for HIV Infected Children greater than or equal to 12 Months of Age

- All HIV infected children greater than or equal to 12 months of age should continue to have regular CD4+ monitoring to determine their need for PCP prophylaxis (Table 3.4.3).
- HIV infected children and children whose infection status has not been determined should be evaluated at 12 months of age to determine their need for continued PCP prophylaxis.

PCP prophylaxis should be continued after 12 months of age for HIV infected children who have had any CD4+ measurement during the first 12 months of life indicating severe immunosuppression (i.e. a CD4+ count of less than 750 cells/uL or a CD4+ percentage of less than 25%). Prophylaxis should be discontinued at 12 months of age for HIV infected children whose CD4+ measurements have been adequately monitored (Table 3.4.3) and have remained higher than these levels. PCP prophylaxis should also be discontinued for any child who is diagnosed as not being infected with HIV.

- Children who have received PCP prophylaxis from 12 to 24 months of age should be evaluated again at 24 months of age, and prophylaxis should be continued for those children who have had any CD4+ measurement indicating severe immunosuppression (i.e. a CD4+ count of less than 500 cells/uL or a CD4+ percentage of less than 15%). Prophylaxis should be discontinued at 24 months of age for HIV infected children whose CD4+ measurements have been adequately monitored (Table 3.4.3) and have remained higher than these levels.
- HIV infected children greater than or equal to 12 months of age who are not receiving prophylaxis (e.g. those children whose infection was not identified previously or whose PCP prophylaxis was discontinued) should begin PCP prophylaxis if their CD4+ measurement indicates severe immunosuppression.
- Initiation or continuation of prophylaxis should also be considered on a case-by-case basis for HIV infected children greater than or equal to 12 months of age who might otherwise be at risk for PCP, such as children with rapidly declining CD4+ counts or percentages or children with severely symptomatic HIV disease.

Prophylaxis Against PCP Recurrence

- HIV infected children who have had an episode of PCP should receive lifelong PCP prophylaxis to prevent recurrence, regardless of CD4+ measurement or clinical status.

Recommended Chemoprophylaxis Regimens (Table 3.4.3)

- The recommended PCP chemoprophylaxis regimen for children is trimethoprim/ sulfamethoxazole (TMP-SMX). When initiating TMP-SMX prophylaxis, a baseline complete blood count, differential count, and platelet count should be obtained. These measurements should be repeated monthly while the child is receiving prophylaxis.

If TMP-SMX is not tolerated, alternative regimens should be followed. On the basis of recently compiled pharmacokinetic data, the revised recommended dosage of dapsone as an alternative regimen is 2 mg/kg/day. These data indicate that peak serum concentrations for children receiving chronic dosing of dapsone at 1mg/kg/ dose average 1.84 ug/mL, compared with average peak concentrations of 4.65 ug/mL for adults receiving the standard dose of 100 mg/day. The increased dose of dapsone is recommended so that peak concentrations will approach concentrations achieved at dosages recommended for adults.

PCP prophylaxis is an approved labeling indication by the US Food and Drug Administration for oral TMP-SMX but not for various other alternative regimens for PCP prophylaxis. However, clinicians should be aware that some children have developed PCP despite the use of recommended prophylaxis.

WHO Recommendations for Co-trimoxazole Prophylaxis for Infants and Children (Tables 3.4.3 to 3.4.6)

Table 3.4.3: Initiation of co-trimoxazole prophylaxis in infants and children

Situation			
HIV-exposed infants and children[a]	*Infants and children confirmed to be living with HIV[b]*		
	<1 year	*1-4 years*	*5 years*
Co-trimoxazole prophylaxis is universally indicated, starting at four to six weeks after birth and maintained until risk of HIV transmission ceases and HIV infection is excluded	Co-trimoxazole prophylaxis is indicated regardless of CD4 percentage or clinical status[C]	WHO clinical stages 2, 3 and 4 regardless of CD4 percentage OR Any WHO stage and CD4 <25%	Follow adult recommendations

OR

Universal option: prophylaxis for all infants and children born to mothers confirmed to be or suspected of living with HIV. This strategy may be considered in settings with a high prevalence of HIV, high infant mortality due to infectious diseases and limited health infrastructure.

a. Defined as a child born to a mother living with HIV or a child breastfeeding from a mother living with HIV until HIV-exposure stops (six weeks after complete cessation of breastfeeding) and infection can be excluded.

b. Among children younger than 18 months, HIV infection can only be confirmed by HIV viral testing.

c. Once a child is started on co-trimoxazole, prophylaxis should continue until five years of age regardless of clinical symptoms or CD4 percentage. Specifically infants who begin co-trimoxazole prophylaxis before the age of one year and are subsequently asymptomatic and/or have CD4 levels ≥ 25% should remain on co-trimoxazole prophylaxis until they reach the age of five years.

Table 3.4.4: Dosages of commonly used co-trimoxazole formulations for infants and children living with or exposed to HIV

Rcommended daily dosage[a]	*Suspension (5 ml of syrup 200 mg/40 mg)*	*Child tablet (100 mg/20 mg)*	*Single-strength adult tablet (400 mg/80 mg)*	*Double-strength (800mg/160mg)*
<6 months or <5 kg–100 mg sulfamethoxazole/ 20 mg trimethoprim	2.5 ml	One tablet mixed with feed or small amount of milk or water	¼ tablet, possibly mixed with feed or small amount of milk or water[b]	-
6 months-5 years or 5-15 kg–200 mg sulfamethoxazole/ 40 mg trimethoprim	5 ml[c]	Two tablets	Half tablet	-
6-14 years or 15-30 kg–400 mg sulfamethoxazole/ 80 trimethoprim	10 ml[c]	Four tablets	One tablet	Half tablet
>14 years or >30 kg–800 mg sulfamethoxazole/ 160 mg trimethoprim	-	-	Two tablets	One tablet

Frequency- once a day

a. Some countries may use weight bands rather than age to determine dosing.

b. Splitting tablets into quarters is not considered best practice. This should be done only if syrup is is not available.

c. Childern of these ages (6 months-14 years) may swallow crushed tablets.

Source: World Health Organization. Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults. Recommendations for a public health approach. Geneva, WHO, 2006:15. http://www.who.int/hiv/pub/guidelines.pdf[a]

Alternative regimens if TMP-SMX is not tolerated

- Dapsone*
  2 mg/kg (not to exceed 100 mg) administered orally once daily
- Aerosolized pentamidine* (children ≥ 5 years of age) 300 mg administered via Respirgard II inhaler monthly.

* If dapsone nor aerosolized pentamidine is tolerated, some clinicians use intravenous pentamidine (4 mg/kg) administered every 2 or 4 weeks. Children with a history of treated PCP should be administered secondary co-trimoxazole prophylaxis with the same regimen recommended for primary prophylaxis.

8. Growth Monitoring

Sequential assessment of growth and physical development is of particular importance. A small number of HIV exposed neonates are born with low birth weight, but most infected infants grow normally in utero and cannot be

Table. 3.4.5: Summary of recommendations for discontinuing primary co-trimoxazole prophlaxis among infants and children

Target Population	*Recommendations*
HIV-exposed children	Discontinue co-trimoxazole prophylaxis after HIV infection is excluded
Infants and children living with HIV	Maintain on co-trimoxazole prophylaxis until the age of five years. irrespective of clinical and immune response Children older than five years can be reassessed and consideration given to discontinuing co-trimoxazole prophylaxis in accordance with the recommendations for adults and adolescents

The general recommendation is that secondary co-trimoxazole prophylaxis should not be discontinued, irrespective of the clinical and immune response to ART.

Source: World Health Organization, *Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults. Recommendation for a public health approach. Geneva,* WHO, 2006. Available at: http://www.who.int/hiv/pub/guidelines/ctxguidelines.pdf (accessed on 28 July 2009)."

Table 3.4.6: Co-trimoxazole prophylaxis for children less than 5 years–adopted from international center for AIDS care and treatment programs, Columbia University

Cotrimoxazole Prophylaxis for Infants and Children; Dosing Recommendations: 4 mg/kg per day
Trimethoprim/sulfamethoxazole
CTX/SMZ, Contrimoxazole, Septrim®, Bactrim®

Weight in kilograms	*8 mg/ml suspension (daily dose in milliliters)*	*Single-strenth tablets (80 mg TMP/400 mg SMZ)*
3-4.9 kg	2 ml daily	
5-6.9 kg	3 ml daily	
7-9.9 kg	4 ml daily	½ single-strength tab daily
10-11.9 kg	5 ml daily	½ single-strength tab daily
12-14.9 kg	7 ml daily	1 single-strength tab daily
15-16.9 kg	8 ml daily	1 single-strength tab daily
17-19.9 kg	9 ml daily	1 single-strength tab daily
20-24.9 kg	11 ml daily	2 single-strength tab daily
25-26.9 kg	14 ml daily	2 single-strength tabs* daily
30-34.9 kg	17 ml daily	2 single-strength tabs* daily
35-40 kg	20 ml daily	2 single-strength tabs* daily

Sourse: International center for AIDS and treatment programs, Columbia University

distinguished from uninfected infants by size at birth. All children should have sequential measurements of growth. Patients should have serial assessments of neurological and development status. Developmental assessment should be conducted at each visit which includes cognitive, motor, language and social skills.

9. Physical Examination

Examine for lymphadenopathy, hepatosplenomegaly, oral thrush, seborrheic dermatitis, ear infection and wasting.

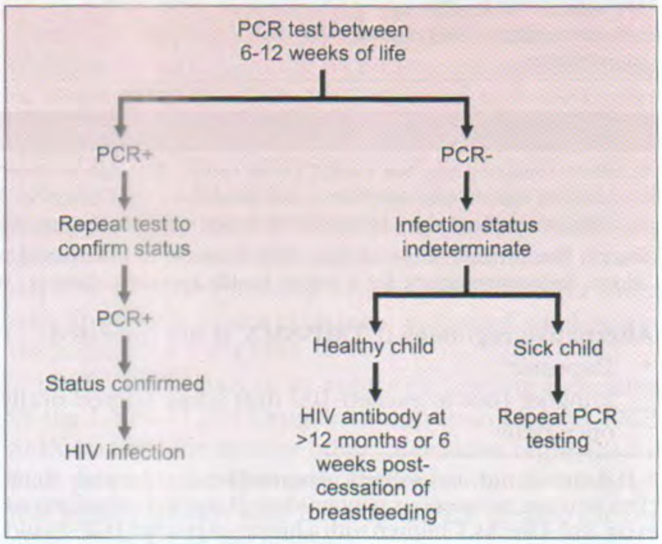
10. Determining HIV Status in HIV Exposed Children

Since there is passive transfer of maternal antibodies to the fetus which lasts for 9- 15 months of age, HIV Elisa testing is not diagnostic at birth. The following tests needs to be conducted to determine HIV infection.

Four to Six weeks of age-HIV DNA/RNA PCR (Flow Chart 3.4.1)

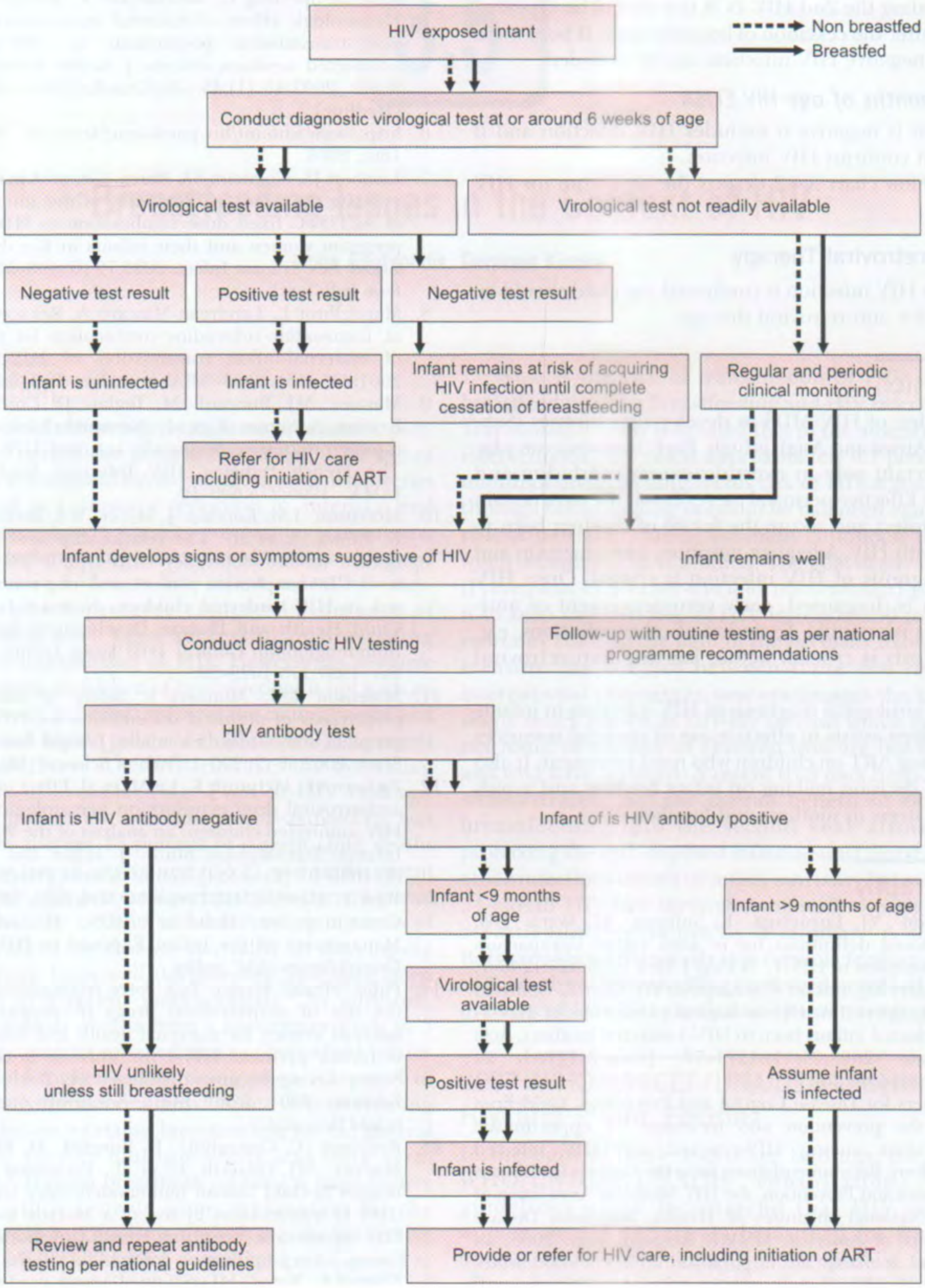
Repeat the test at 4-6 months of age.

Flow chart 3.4.1: PCR test between 6-12 weeks of life



International center for AIDS care and treatment programs. Columbia University

Flow chart 3.4.2: Testing sequence for inital and subsequent visits of HIV exposed infant



If the mother is formula feeding HIV infection can be excluded if the PCR is negative. If the mother is breastfeeding the 2nd HIV PCR test should be repeated 6 weeks after the cessation of breastfeeding. If both these tests are negative HIV infection can be excluded.

15-18 months of age-HIV ELISA

If the test is negative it excludes HIV infection and if positive it confirms HIV infection.

The Flow chart 3.4.2 depicts the algorithm for HIV testing

11. Antiretroviral Therapy

Once the HIV infection is confirmed the child should be referred for anti-retroviral therapy.

Conclusion

The burden of HIV/AIDS in developing countries (Sub-Saharan Africa and Asia) is high. Early diagnosis can play an important role in averting excess morbidity and mortality. Effective perinatal prevention is the most certain way to protect and secure the future of children born to women with HIV. Adequate nutrition, immunization and early diagnosis of HIV infection is crucial. Once HIV infection is diagnosed, early commencement of anti-retrovirals is essential. Exclusion of other infections, e.g: Tuberculosis is crucial, before starting anti retroviral therapy.

Early virological diagnosis of HIV infection in infants and children assists in effective use of essential resources by targeting ART on children who need treatment. It also assists in decision making on infant feeding and avoids needless stress in mothers and families.

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3.5

Breastfeeding Issues in the Context of HIV

Anna Coutsoudis, Gurpreet Kindra

Introduction

Mother-to-child transmission can occur antenatally, perinatally and during the postpartum period. The use of antiretroviral drugs and elective cesarean section deliveries has resulted in a dramatic reduction in antenatal and perinatal transmission whereas postpartum transmission remains a challenge. In well-resourced settings with good health services and very low infant mortality rates, programs which promote complete avoidance of breastfeeding have been successful in preventing postpartum transmission of HIV. However, in resource limited settings, avoidance of breastfeeding is not such an obvious strategy as breastfeeding is the cultural norm and one of the well known pillars of child survival. The recent Lancet Child Survival series[1] reinforces the overriding importance of breastfeeding. Even in HIV endemic countries, promotion of exclusive breastfeeding was estimated to prevent 13 percent of current child deaths whereas the use of nevirapine (NVP) and replacement feeding would only prevent 2 percent of the current global child deaths. The benefits of breastfeeding in terms of reducing infectious disease mortality in developing countries have been well documented and have been reinforced in a recent meta-analysis.[2] In addition, secondary analysis of data from a multicenter study in 3 developing countries revealed that nonbreastfeed infants had a 10-fold higher risk of dying when compared to predominantly breastfed infants.[3] Apart from preventing infectious disease mortality, breastfeeding for the general population carries multiple short and long term advantages.[4] Human breastmilk contains a large variety of factors which provide some explanation for the immunological mechanisms underlying the protective benefits of breastmilk against enteric infections as well as chronic diseases later in life.[5] In addition to individual health benefits, there are economic and social benefits due to savings from not needing to purchase breast milk alternatives for the child and decreased health care costs due to lowered rates of infant disease.

What is the risk of transmission of HIV through breastfeeding? The Breastfeeding and HIV International Transmission Study estimated that in the absence of any interventions, this risk is approximately 0.7 percent per month of breastfeeding.[6] This risk of HIV transmission through breastfeeding needs to be balanced against the risk of mortality due to common childhood illnesses when breastfeeding, is avoided. The goal of any PMTCT (Prevention of Mother-to-child transmission) program is to keep children free of HIV infection and to reduce mortality risks. In the light of the necessity to be able to measure the balance between these two risks the international community now encourages the use of a single index known as *HIV-free survival* which gives the net result of number of children who are not infected and who have survived. A recent trial data from Zambia demonstrated that the overall benefit of extended breastfeeding into the second year afforded by protecting the HIV-exposed infant against diarrheal and other infectious causes of infant mortality led to similar 24-month HIV-free survival compared to early abrupt breastfeeding cessation by 4 months.[7] A study in Botswana showed similarly that formula feeding relative to 6 months of breastfeeding conferred no added benefit in terms of HIV-free survival at 18 months of age.[8]

2007 WHO/UNICEF/UNAIDS Guidelines of HIV and Infant Feeding

In the light of these and other findings, the expert WHO/UNICEF/UNAIDS consultation[9] issued guidelines which recommend that HIV infected women should exclusively breastfeed for 6 months unless replacement feeding is acceptable, feasible, affordable, sustainable and safe (AFASS Criteria). Interpreting these guidelines for individual countries has not always been easy. Appendix 3.5.1 for an example, of an algorithm which has been developed based on South African research which is used by

counselors to help mothers decide on whether they satisfy AFASS criteria for safe formula feeding. In Appendix 3.5.2 we discuss some case histories around the issue of infant feeding, choices taken from our HIV care and treatment program in Durban, South Africa.

For mothers who do not meet AFASS criteria for safe formula feeding the best option is breastfeeding. Nevertheless effective interventions to reduce the MTCT risk from breastfeeding remains an urgent public health priority.

Four General Strategies have been Proposed to Reduce the Risk of Postpartum Breastfeeding HIV Transmission

Exclusive Breastfeeding During the First 6 Months

At the recent WHO technical consultation on HIV and Infant feeding[9] evidence from four studies was provided and it showed conclusively that exclusive breastfeeding for up to 6 months is associated with a two to four fold decreased risk of HIV transmission compared to non-exclusive breastfeeding. In the light of this evidence, the final deliberations at the consultation recommended that even in areas of high HIV prevalence that governments and other stakeholders should revitalize breastfeeding protection, promotion and support in the general population. As pointed out by Holmes and Savage, although exclusive breastfeeding is not currently widely practiced in the developing world, this can be changed by providing mothers with skilled support from well trained, lay infant-feeding counselors.[10] The onus is, therefore, on policy makers and health care workers to assist mothers to practice exclusive breastfeeding. Corporate companies also have a responsibility to desist from unscrupulous marketing practices that undermine exclusive breastfeeding protection, and governments should make every effort to legalize the Code of Marketing of Breast Milk Substitutes.[11]

Flash Heating of Expressed Breastmilk (HTEBM)

Flash Heating methodology was first developed by Chantry et al.[12] Flash heating was shown to be capable of inactivating "spiked" cell-free HIV-1 as detected by reverse transcriptase activity.[13] Additionally, flash heating inactivated HIV in naturally infected breastmilk samples collected from HIV positive mothers in South Africa.[14] Pilot data suggested limited negative impact of Flash-heat on vitamins and proteins[15] and work on naturally infected samples from women in South Africa showed similar limited negative impact.[16] Flash heating is capable of eliminating pathogenic and nonpathogenic bacteria and an 8-hour storage period outside the refrigerator does not result in a significant increase of bacteria.[17] Immunological studies were conducted in breastmilk samples from HIV infected women in South Africa before and after flash heating. Flash heating resulted in a decrease of 20 percent in total IgA and 33 percent of total IgG in the breastmilk. Similar decreases were seen in anti-HIV-1 gp120 IgG, antipneumococcal polysaccharide and antipoliovirus IgA. Therefore the majority of breastmilk's immunoglobulin activity survives flash heating, suggesting flash heated breastmilk is immunologically superior to breastmilk substitutes.[18] See Appendix 3.5.3 for the methodology as used in South African settings.

How acceptable is this method? A qualitative study was conducted in Zimbabwe to assess attitudes of heat-treating breastmilk.[19] The 77 respondents (mothers, fathers, grandmothers, and birth attendants) in 13 focus groups were initially skeptical, but education that the method could destroy HIV and further discussion led the majority of participants to conclude that if nutritious and safe, heated breastmilk could be a viable, sustainable, and low cost alternative to formula in their communities. Similar studies in South Africa have shown that with the correct promotion and support it would also be an acceptable method.[20]

Unpublished studies from Durban have shown it to be feasible and there are ongoing studies in Zimbabwe and Tanzania examining the feasibility of this method.

Use of Maternal HAART During Breastfeeding

Maternal prophylaxis with HAART (highly active antiretroviral therapy) aims to reduce the risk of transmission primarily by reducing the viral load in breast milk. Additionally transfer of antiretrovirals (ARVs) to the infant through breast milk ingestion also occurs, which could provide some indirect ARV prophylaxis to the infant. There are recent encouraging observational data suggesting a beneficial role for maternal HAART given in the third trimester up to 6 months postpartum for prevention of breastfeeding transmission. This includes 4 open-label observational studies of maternal HAART given during the third trimester through cessation of breastfeeding (up to 6 months) from Kenya, Tanzania, Rwanda, and Mozambique.[21-24] At the International AIDS Society (IAS) meeting (Cape Town, July 2009) data were presented that support the use of maternal HAART in 2 randomized controlled trials. The Mma Bana study from Botswana, compared a protease inhibitor (PI) based HAART regimen comprising Zidovudine (AZT), Lamivudine (3TC), Lopinavir (LPV) and Ritonavir (RTV) to a triple nucleoside reverse transcriptase inhibitor (NRTI) regimen, started between 24-26 weeks for up to 6 months of exclusive breastfeeding, and found overall transmission rates of 0.4 percent for the PI based HAART

and 1.8 percent for NRTI based ART with an overall transmission rate of 1 percent. The second study, the BAN (breastfeeding, antiretroviral and Nutrition) study from Malawi, was a large 2 ´ 3 factorial design study. In this study, all mothers and infants received single dose NVP (sdNVP) plus 7 days of ZDV/3TC followed by randomization into one of three groups: maternal HAART comprising AZT/3TC/LPV/RTV for up to 7 months of exclusive breastfeeding; infant NVP daily; and a maternal nutrition supplementation arm. Findings indicated that extended maternal HAART were superior to the one-week control arm: at 28 weeks post delivery, the postnatal transmission rates among infants uninfected at birth were 3.0 percent for the extended maternal HAART arm, compared to 6.4 percent for the control arm. At 28 weeks, HIV free survival was also significantly better for both extended maternal HAART arm (4.7%) when compared to the control arm (7.6%).

However, as promising as the strategy of using maternal HAART appears to be, it is important to note that infants who become infected despite maternal HAART may have virus with drug resistance mutations. In the KiBs (Kisumu breastfeeding study) study in Kenya,[21] ARV drug resistance (both NRTI and NNRTI mutations) emerged during the breastfeeding period among 67 percent of the 24 infants who became infected despite maternal HAART; in general, resistance was not detected on the initial positive DNA PCR test but at subsequent testing, suggesting resistance could be due to transfer of ARV drug from mother to the infant via breast milk in the presence of actively replicating virus in the infant.[25] Resistance mutations to NRTI drugs were detected in 4 of 6 (66%) infants and to NNRTI (non-nucleoside reverse transcriptase inhibitor) drugs in 6 of 6 (100%) infants whose mothers took NVP-based HAART; resistance mutations to NRTI drugs were detected in 10 of 10 (100%) infants and to PI drugs in 0 of 10 (0%) infants whose mothers took nelfinavir-based HAART.

Finally, an unanswered question is: What is the impact on the mother's health/progression to disease if HAART used for breastfeeding transmission prophylaxis is discontinued when breastfeeding is discontinued?

Use of Infant ARV Prophylaxis During Breastfeeding

The infant ARV prophylaxis strategy aims to protect the infant during the period of HIV exposure during breastfeeding. A phase I/II study of 6 months of infant NVP prophylaxis (HIVNET 023) established the dosing and safety of the daily NVP dosing of HIV exposed infants.[26] Provision of infant NVP through the first 6-14 weeks of breastfeeding has been shown to reduce postnatal HIV transmission in the six week extended-dose nevirapine (SWEN)[27] and in the post-exposure prophylaxis of the infant (PEPI)-Malawi trials[28] compared to the control arm interventions of sdNVP or sdNVP plus one week of infant AZT, respectively, used in the two trials. The SWEN study carried out in Uganda, Ethiopia, and India reported a significant 50 percent reduction in postnatal HIV transmission at age 6 weeks for infants in the study arm who received 6 weeks of daily infant NVP compared to the sdNVP regimen (6 week postpartum transmission rate of 2.5 % versus 5.3% respectively, $p = 0.009$), although this benefit was no longer statistically significant by 6 months (however, 6-month HIV-free survival remained significantly better in the extended infant NVP study arm). The PEPI-Malawi study reported a 67 percent reduction in postpartum transmission at 6 and 14 weeks for infants who were randomized to receive 14 weeks of either daily infant NVP or daily infant NVP/AZT compared to sdNVP plus 1 week of daily AZT and a persistent significant 50 percent reduction in postnatal transmission at age 9 months. There were no significant differences in efficacy between the daily NVP and combination NVP/AZT arms, but infants in the combination arm were more likely to have adverse events that were possibly associated with the study drug, predominantly neutropenia. The BAN study in Malawi, mentioned earlier, which tested the efficacy of maternal HAART also tested a control regimen of intrapartum sdNVP plus 7 days of AZT/3TC to the infant against daily NVP prophylaxis given for up to 7 months of exclusive breastfeeding. Findings indicated that extended infant NVP prophylaxis was superior to the one-week control arm: at 28 weeks postdelivery, the postnatal transmission rates among infants uninfected at birth were 1.8 percent for the extended infant NVP arm compared to 6.4 percent for the control arm. At 28 weeks, HIV free survival was also significantly better in the extended infant prophylaxis arms (2.9%) when compared to the control arm (7.6%). There is also an ongoing efficacy trial (HPTN 046) which is comparing 6 months of daily infant NVP to a control arm of 6 weeks of daily infant NVP based on the SWEN trial findings.

As with the maternal HAART intervention, there are some possible negative impacts which need to be considered, *viz*. the possibility of increased resistance to NVP. In the SWEN study, infants who became infected despite extended NVP prophylaxis and were infected during the period of prophylaxis had an increased risk of selection for and persistence of NVP resistance mutations.[29] However, infants who became infected after the period of NVP prophylaxis ended (after age 6 weeks) were less likely to have NVP resistance than infants who were infected *in utero*, peripartum or during the first 6 weeks of breastfeeding.[30] Safety issues of NVP appear to be minimal and most studies have reported neutropenia to be the most serious side effect.

While direct comparison between studies is difficult due to differing populations and different durations of breastfeeding, based on the above data, both maternal HAART and infant NVP prophylaxis appear promising as public health approaches to reducing the risk of HIV transmission among HIV infected breastfeeding women who do not require treatment for their own health while preserving the beneficial effects of breast milk on overall infant survival in resource limited settings. However to date, the relative risks and benefits of these two strategies (i.e. maternal HAART versus infant ARV prophylaxis) have not been directly compared. Additionally, the safety of continuing either maternal or infant prophylaxis to allow periods of breastfeeding beyond 6 months warrants investigation. In view of these unanswered questions the NIH/IMPAACT funded study, the PROMISE (promoting mother and infant survival everywhere) trial, has been designed to compare the relative efficacy of daily maternal HAART to infant NVP prophylaxis given for the duration of breastfeeding or up to 18 months postpartum, whichever comes first unless stopped for toxicity, other medical reasons or confirmed infant HIV infection. The trial will have sufficient power to compare the efficacy, tolerability, safety and cost effectiveness of maternal HAART versus infant NVP prophylaxis during the postpartum period of breastfeeding and will provide valuable data to guide decisions on the most appropriate interventions to make breastfeeding safer in terms of transmission of HIV.

The Special Case of Feeding the HIV Infected Infant

Until ARV prophylaxis programs to prevent *in utero* and peripartum transmission are widely used there will still be infants who are born infected. How should we feed HIV infected infants? Historically, there has been reticence around feeding these infants breastmilk as there was the concern that infants will continually be re-exposed. Several studies have been conducted in the last 5 years comparing the outcome of infants who receive breastmilk as opposed to formula feeds. All the studies have shown conclusively that HIV infected infants who are breastfed have less morbidity, take longer to progress to AIDS and have better survival. In view of these finding the WHO/UNICEF/UNAIDS guidelines[9] recommend:

Breastfeeding mothers of infants and young children who are known to be HIV infected should be strongly encouraged to continue breastfeeding for at least 2 years.

Therefore, it is important that all HIV exposed infants are tested by PCR at 6 weeks of age, those children who are found to be HIV infected or on clinical grounds are suspected of being HIV infected should continue receiving breastmilk.

Newly released WHO/UNICEF/UNAIDS Guidelines—30 November, 2009

In view of the recent evidence showing that:

1. Protection, promotion and support of breastfeeding are vital for child survival.
2. Both maternal HAART and infant prophylaxis with NVP are effective in reducing transmission of HIV through breastfeeding.

It was decided by a WHO guideline review committee that they should move ahead and publish new guidelines in spite of the fact that there are still some unanswered questions which are being addressed in the promise study mentioned above. The decision was made that logistically and in terms of less risk of resistance that the best option for protection against breastfeeding transmission would be infant prophylaxis with nevirapine. Furthermore, it was suggested that:

National and regional health authorities should, based on international recommendations and consideration of the socioeconomic and cultural contexts of the populations served by MCH services, the availability and quality of health services, the local epidemiology and main causes of infant and child mortality including HIV prevalence among pregnant women, and maternal and child under-nutrition, decide whether MCH services will:

- Principally promote and support breastfeeding with ARV interventions as the strategy that will most likely give infants born to HIV infected mothers the greatest chance of HIV-free survival
- Principally advise HIV infected mothers known to avoid all breastfeeding as the strategy that will most likely give infants born to mothers known to be HIV infected the greatest chance of HIV free survival.

WHO also undertook to develop an adaptation guide to assist countries with this decision.

Conclusion

Four promising strategies exist to reduce the risk of HIV transmission of HIV during breastfeeding and the challenge is now how we can scale up coverage of such interventions. Addressing this challenge will require the following:

- Political leadership
- Health system improvement—improving amongst other things: access, delivery systems, inequities
- Improved counseling
- Mentoring and supervision of counselors
- Community empowerment, creating demand for quality health care services and delivery

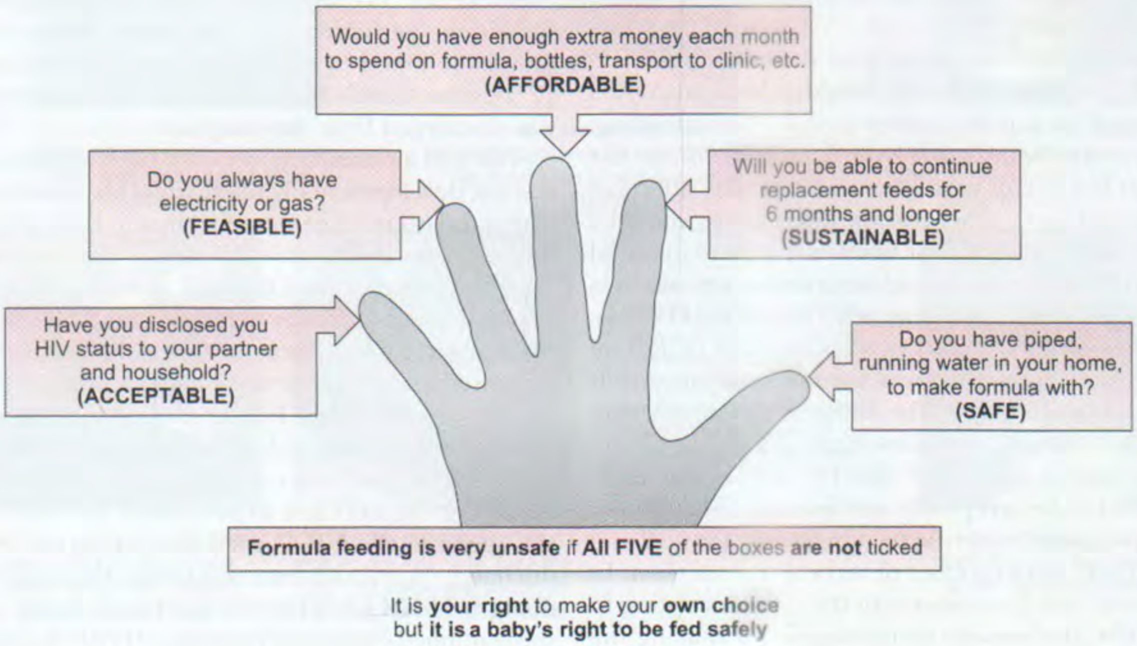
Appendix-3.5.1

Algorithm used to help mothers in South Africa decide if they satisfy the AFASS criteria for safe formula feeding

Exclusive breastfeeding for 6 months before introducing solid foods and continuing to breastfeed for at least 2 years is the healthiest way to feed your baby.

Even if you are HIV-positive, exclusive breastfeeding for 6 months is the best way to feed your baby unless you meet all the AFASS criteria indicated below.

It is important that you understand the risks and benefits of breast and formula feeding, before using the "**AFASS**" hand to help you decide what feeding method is best for you and your baby.



Appendix-3.5.2

Case Studies read /12 as months and /52 as weeks

Formula fed infants

1. NM, term baby. AFASS not fulfilled. Failure to thrive from the start; DNA PCR positive at 6/52. Recurrent admissions for respiratory tract infection; diagnosed with pulmonary TB and died at 6/12 in hospital before starting HAART.
2. LM, term baby. AFASS not fulfilled. DNA PCR negative at 6/52. Died at 9/12 from acute GE with severe dehydration.
3. MD, term baby. AFASS not fulfilled. DNA PCR negative at 6/52. Died at 5/12 from acute GE.
4. TN, term baby. AFASS fulfilled. DNA PCR positive at 6/52. Admitted for acute GE and LRTI twice. Started on HAART at 11/52 of age. Thriving now at 18 months.

Breastfed infants

1. KB, term baby. DNA PCR positive at 6/52. Thrived despite being positive. Diagnosed with Pulmonary TB and started on HAART at 6/12. Mum continued breastfeeding till 2 years of age.
2. TM, term baby. DNA PCR negative at 6/52. Stopped breastfeeding at 3/12. Admitted for acute GE and LRTI subsequently, diagnosed with pulmonary TB. DNA PCR positive at 3/12, regression of milestones. Started on HAART at 6/12, thriving now at 2 years of age, achieving milestones.
3. NN, term baby. DNA PCR negative at 6/52. Stopped breastfeeding at 6/12. Repeat PCR positive at 9/12. Subsequently started on HAART. Thriving now at 15 months.
4. ZS, term baby. DNA PCR negative at 6/52. Stopped breastfeeding at 6/12. Had recurrent episodes of diarrhea on replacement feeding. DNA PCR negative at 9/12. Counseled on substituting to fermented milk and improved.

Discussion

It has been shown beyond doubt that the fulfillment of AFASS criteria is critical to safe replacement feeding (in our case replacement feeds are always formula feeds). The clinician must understand that every mother will want the best for her child and if public health messages state that she must avoid breastfeeding in order to prevent vertical transmission or if any health personnel casts even the slightest doubt in the mother's mind, she will end up mix feeding or worse-diluting the formula (if she has insufficient funds). It is clear from the above case histories that where AFASS criteria are not fulfilled and mothers choose to formula feed it has serious negative consequences for the health of the infant, as seen in case histories 1-3.

When recommending feeds after 6 months the WHO guidelines[9] recommend that we should recheck the AFASS criteria and if not fulfilled, rather continue breastfeeding. However, once the infant is over 6 months of age the infant is at less risk of morbidity and mortality effects of not breastfeeding so other feasible alternatives would be the use of yoghurt (dahi). For families that have financial restraints the best option would be to encourage mothers to express breastmilk and heat treat this milk (HTEBM). The mother could heat and express amounts of 120 ml approximately 5 times a day which would satisfy the needs of a 6-9 month old infant. The infant at this stage would now be also receiving complimentary foods.

In our limited experience with HTEBM at the clinic, it was found to be acceptable and feasible although few mothers continued to do the heat treatment for 9/12 and beyond. There were no cases of vertical transmission. In our in depth case interviews with the mothers opting to use HTEBM, the reasons mothers gave for making the choice was that it was clean, free, they did not need to use bottles and they noticed that their babies were growing well. The facilitating factors included disclosure to their partners, support from their families and encouragement from the feeding counselors and especially the doctors and nurses.

Some Examples of Mothers who used HTEBM

MM had a term baby. Her HIV DNA PCR was negative at six weeks. As the AFASS criteria were not fulfilled, she chose to exclusively breastfeed. At six months, noting that her child was thriving, MM opted to continue using HTEBM along with semi-solids till 10 months. Child's final HIV result was negative and she was discharged from the program.

TB had a term baby. His HIV DNA PCR was negative at six weeks. TB was unemployed being supported by her sister, she too chose to exclusively breastfeed till 6 months followed by HTEBM along with semi-solids till 12 months. Child's final HIV result was negative and he was discharged from the program.

ND had a premature, very low birth weight baby who was not developmentally ready to suckle from the breast. The standard management for these infants who remain in the neonatal intensive care unit is for the mother to express breastmilk and the milk is fed to the infant via nasogastric tube. However in this case, the mother was encouraged to heat treat her breastmilk after she had expressed it and allow it to cool before putting it through the nasogastric tube. In our unit all the utensils are supplied for mothers to heat treat the milk themselves in a special room designated for this. ND continued supplying the HTEBM to her infant for the 2 months she spent in the NICU until the infant was ready for discharge. When she returned home, she said that after doing HTEBM for 2 months she found it very easy and she continued exclusively providing HTEBM to the infant for 6 months after which she switched to formula feeds. The infant is now 15 months, uninfected and growing very well.

Appendix-3.5.3

Flash Heating of Expressed Breast Milk

What you will need:
450 ml Glass bottle—the kind sometimes used for jam or peanut butter and a small 1-litre pot

How to Do it:



1. Make sure that the bottle is clean and wash your hands with soap and water before you start expressing



2. Express breast milk into the clean jar (between 50 and 120 ml)—not more than ¼ of the volume of bottle



3. When you have expressed enough milk, put the lid on the bottle and place the bottle in the pot



4. Pour cold water into the pot making sure that the water level is two fingers above the milk level



5. Put the pot with the jar of milk on the hot plate, take the lid of the bottle and switch on hot plate to the highest level

6. When the water is boiling rapidly, take the pot off the stove. Remove the bottle from the pot and put the lid on the bottle and allow the milk to cool. If you want to cool the milk quickly, put the bottle in cold water



7. Pour the breast milk into a clean cup and feed the milk to the baby from the cup

Key Messages

- Breastfeeding is a pillar of child survival and should only be replaced by HIV infected mothers when formula feeding is acceptable, feasible, affordable, sustainable and safe.
- HIV infected women who are breastfeeding should practice exclusive breastfeeding in the first 6 months as this has been shown to substantially reduce the risk of HIV transmission.
- The risk of breastfeeding transmission can be reduced by several strategies, viz. HAART to the mother; NVP prophylaxis to the infant; and heat treatment of expressed breastmilk.

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3.6

Perinatal HIV and Tuberculosis Infection and Management

Mirium Adhikari

Introduction

Approximately 250,000 African women die during pregnancy, delivery and the puerperium each year. In Sub-Saharan Africa, more than the obstetric causes of death, infectious diseases make a major contribution to maternal mortality rates.[1] The number of cases of tuberculosis (TB) in Sub-saharan Africa has increased progressively and up to 70 percent or more are HIV positive.[2,3]

TB and HIV are independent risk factors for maternal mortality. In Sub-Saharan Africa, 3-4 percent of HIV infected mothers die within a year of parturition.[4,5]

A significant increase in tuberculosis in pregnant women was shown by an increasing caseload from 0.1 percent to 0.6 percent between 1996 and 1998 in Durban, South Africa. Of these mothers with TB, 115 (78.8%) were HIV infected, 26 (17.8%) were uninfected and in 5, the HIV status was unknown. The minimum TB/HIV coinfection rates increased from 36.4 percent in 1996 to 88.3 percent in 1998 ($p<0.001$). The TB prevalence rate for HIV noninfected maternities at King Edward VIIIth Hospital, Durban was 72.9/100,000 and for the HIV infected maternities 774/100,000 with a relative risk of TB due to HIV infection of 10.62. The attributable fraction of TB related to HIV infection in these pregnant women was 71.7 percent. The mortality rate in the TB infected mothers was 103/100,00 with 14 of the 15 mothers who died being HIV infected.[6] In a two year retrospective study of maternal deaths at a teaching hospital in Lusaka, Zambia, 58 percent of the deaths were due to infections, malaria (30%), TB (25%) respiratory infections (22%) and other HIV associated opportunistic infections.[7] In a hospital based, five year study at tertiary level in Johannesburg, South Africa, 106 maternal deaths occurred in 36,708 deliveries. Seventy percent of deaths were HIV related-mainly TB and pneumonia. Maternal mortality ratios in HIV infected women were 776 per 100,000, 6.2 fold higher than HIV negative women, 124 per 100,000. Screening for TB in pregnancy was seen as essential by the authors but was not undertaken routinely.[8]

In an autopsy study of 171 maternal deaths in Mozambique, 56 percent of the deaths were due to nonobstetric causes, mostly HIV/AIDS related infections, lung sepsis, meningitis, malaria and TB.[9]

Since 1990, the number of TB cases have increased significantly globally and 75 percent of the cases are HIV infected.[10]

Gender Differences

Although TB is seen as a disease of men, there has been a global increase in the number of women with TB, intersecting with the HIV epidemic. The age groups of 15 to 24 years and 25 to 29 years are the child bearing years and the mortality of this age range has increased.[11,12] Epidemiological evidence indicates there are gender differences in pulmonary disease with respect to a number of aspects such as risk, pathogenesis and histology. This applies to TB, lung malignancy, asthma and chronic lung disease.[13] Smoking, may to some extent, explain the gender differences in the global tuberculosis epidemic and in severe early-onset chronic obstructive pulmonary disease.[14,15]

Pregnancy may carry burdens of socioeconomic and sociomedical issues which hamper access to care antenatally and a possible lack of trained health professionals attending deliveries.[16] In addition, epidemiological evidence suggest that there are differences between the sexes, reflected in the data on exposure to infection and in the susceptibility to develop active disease after infection.[17] There is also evidence that men are more likely than women to be positive on tuberculin skin testing and to be smear-positive on sputum microscopy.[18,19]

Tuberculosis in Pregnancy

Tuberculosis may be exacerbated during pregnancy for a number of reasons including poor nutrition, immunodeficiency and/or coexisting disease.[11] In 1975 Schaefer et al reported a mortality approaching 40 percent in pregnant women with advanced tuberculosis.[20] The immune response in pregnancy shifts the cell mediated Th1 responses towards Th2 antibody help responses which allows the fetus to tolerate nonself antigens. The key cell involved in the tolerance of TB is the CD4 lymphocyte and thus, pregnancy allows the progression of TB.[21,22] This explains the reasons for a greater proportion of pregnant women being TB smear-positive.[23]

The Impact of the Burden of Disease in Sub-Saharan Africa

The impact and extent of tuberculosis in pregnant women was first recognized in South Africa when neonates were infected with tuberculosis.[24]

The Sub-Saharan African region has the highest incidence rates of tuberculosis at 356 per 100,000 population per year according to WHO.[17] In 1999, the South African province of KwaZulu Natal was shown to have an TB incidence rate of 813/100,000 and the HIV seroprevalence at antenatal clinics was a dramatic 40 percent.[3,25]

In the 1990s, TB emerged as a cause of 'chronic lung disease' in the newborns in Durban, South Africa.[24] The neonatal disease reflects the maternal disease which should be detected antenatally and treated in the mother.[6,26] One of the difficulties experienced in Durban and Malawi was the staff concerns about workload.[27]

Vertical Transmission of TB

The presence of exposure does not translate to disease and there is difficulty in diagnosing disease.[28] Progression from infection to disease is highest in the first year of life.[29]

The vertical transmission in the Durban, South Africa study was 15 percent within the first three weeks. Babies whose mothers are diagnosed with TB antenatally present in first week of life with disease and those babies whose mothers with a diagnosis of TB late in pregnancy, present in the third week of life. Babies born to mothers who received no prenatal care had a higher relative risk of developing TB than those who received care (5.6 vs 2.6). Nonadherence to therapy was an important factor in a few cases. Mothers who were sputum smear-negative or with culture negative sputum samples, did not preclude transmission.[30]

Clinical Features of TB in Mothers

The clinical presentation of TB in pregnant and non-pregnant women is similar.[31,32] The symptoms of fatigue and malaise are common in pregnancy and are the early signs of TB. This may be misleading and lead to a delay in diagnosis. Signs and symptoms may vary from no complaints to an abnormal chest radiograph.[31] Clinical features may be mild with cough, fever and fatigue to obvious signs with weight loss, hemoptosis.[23,33,34] The pulmonary form of the disease is the commonest in pregnant women. Extrapulmonary TB may occur in 10 to 15 percent of cases.[35] Pleural effusion was the commonest form of extrapulmonary TB in the study from South Africa.[30]

The diagnosis of TB in the mother is dependent on an awareness in the antenatal period, a good history is crucial in addressing the following points:

- Persistent cough for two weeks or more
- Unresolving pneumonia
- Previous history of TB
- Current anti TB therapy
- TB contact at home
- HIV status

Four months of therapy appears to protect the newborn from transmission but compliance and adherence to therapy is important.[36]

Investigations in the Pregnant Woman

- Sputum for AFBs on smear microscopy
- Culture of sputum for AFB
- Radiological features of TB
- Histological evidence form any site including an endometrial sample (within 72 hours of delivery)

In areas of widespread TB infection rather than disease, the tuberculin skin test is unhelpful in adults. Extrapulmonary TB should be sought:

- If the diagnosis is suspected in the mother with a clear chest radiograph
- The diagnosis is made in the newborn or
- The mother has a positive HIV test

Pathogenesis of Perinatal TB

Pulmonary TB and extrapulmonary TB including genital infection exposes the neonate to the development of TB in the antenatal, intrapartum and postpartum period.

The Newborn may Acquire TB

- *In utero* through hematogenous spread via the umbilical vessels, aspiration or ingestion of infected amniotic fluid

- Intrapartum through aspiration or ingestion of tuberculous amniotic fluid or cervicovaginal secretions at birth
- Postpartum acquisition of AFBs through inhalation or ingestion from an infectious source, usually the mother.[37]

The strain of mycobacterium in the newborn is not specific to the newborn but common to that of the mother whether transmitted congenitally or postnatally.[38] Risk factors for increasing vertical transmission of TB from mother to baby include miliary TB, untreated TB. Late pregnancy or postpartum diagnosis was significantly associated with detection of bacilli in the newborn.[36]

Diagnosis of TB in the Newborn

The maternal history is the most important aspect for the prevention and detection of this disease in the newborn. Therefore, a high index of suspicion is essential if cases are not to be missed. A positive maternal HIV status increases the likelihood of TB infection in the mother.[39,40] The symptoms of TB in the newborn occur most commonly in growth retarded, low birth weight infants. As with most infections, the signs are nonspecific with lethargy, poor feeding, feed intolerance, poor weight gain, unresolving or recurrent pneumonia. The pneumonia may be present at birth. The disease manifests more overtly in the second or third week of life. Typically they have respiratory problems, hepatosplenomegaly and lymphadenopathy.[24,41] Other clinical presentations include ear discharge, skin lesions, seizures, jaundice, paravertebral abscess and hematological derangements. The disease, although chronic, may present acutely and the diagnosis may be missed.[37,42]

Investigations in the Newborn

Having established the maternal history and noted the clinical course of the baby, the baby should be investigated. Microscopy and cultures of three gastric aspirates, induced sputum, tracheal aspirates if mechanically ventilated, cerebrospinal fluid and pleural fluid aspirate if a pleural effusion is seen on the chest radiograph. The three early morning gastric washings are taken before the first feed of the day and placed in 1 percent sodium bicarbonate buffer for transport to the laboratory. The chest radiograph rarely demonstrates the typical features of TB. Tissue samples such as liver and lymph node biopsy may be indicated on clinical grounds. Ear discharge and skin lesions, if present, should be cultured.[37] The induced sputum produces a higher yield of smear-positive samples for mycobacterium than gastric aspirates.[43] Bronchoalveolar Lavage (BAL) an important investigation in children has been extrapolated to the newborn.[44] The diagnosis of TB using DNA amplification (Polymerase chain reaction PCR) has been shown to be of value.[45] A blood culture for TB is available.

Investigations in the Newborn
- Chest radiograph
- Early morning gastric washings × 3
- Induced sputum
- Endotracheal aspirate if mechanically ventilated
- Cerebrospinal fluid
- Liver and lymph node biopsy
- Culture of ear discharge or skin lesions
- Bronchoalveolar lavage
- TB PCR
- Blood culture for TB

Management of the TB Exposed Newborn

The risks of transmission to the newborn have been outlined above. The exposed newborn may be asymptomatic or symptomatic.

Management of the Asymptomatic Newborn

If the newborn is asymptomatic and the mother is considered to have sensitive Mycobacterium then the infant should receive prophylaxis as soon as the investigations have been completed. Prophylaxis is isoniazid (INH) 10 mg/kg/day and rifampacin (RIF) 10 mg/kg/day for 3 months.[46] The Bacille Calmette-Guérin vaccine (BCG) is withheld till completion of the period of prophylaxis. At the end of the 3 months the chest radiograph should be repeated. In addition, the baby should be screened for other coinfections such as cytomegalovirus, herpes simplex and herpes zoster. If, during the period of prophylaxis, the infant develops signs that suggest TB or the cultures are positive, full anti-TB therapy should be commenced and continued for 6 months. In HIV and TB high prevalence areas, prophylaxis may not offer protection against acquisition of TB. If the maternal HIV status is unknown the mother should be tested.

Management of the Symptomatic Newborn

A differential diagnosis of HIV, syphilis, cytomegalovirus, congenital herpes and atypical pneumonia (*Mycoplasma pneumoniae*) should be considered in infants who present with the physical signs indicated above.[29] On clinical suspicion, anti-TB therapy should be commenced once the relevant samples have been taken for tuberculosis.

Standard WHO–recommended drug regimens are INH 10 mg/kg/day, RIF 10 mg/kg/day and pyrazinamide 20 mg/kg/day for two months followed by a four-month course of INH and RIF. Therapeutic response is determined by the regression of clinical signs, weight gain, improved appetite and radiological resolution where applicable.

If the baby is HIV PCR positive, following two weeks of anti-TB therapy or longer and depending on the clinical condition of the infant and if there are no side effects of treatment, ARVs may be commenced. The process of commencing ARVs is very difficult, particularly if the mother is not on therapy. The mother has to be in a clinically reasonable condition to manage her baby. It is important to train another individual in the household to assist the mother. Experience with respect to the ARVs and their dosages in the newborn is increasing.

Zidovudine (AZT) is the ARV that has been most studied in the newborn followed by lamivudine.[47] Zidovudine is given at a dosage of 2 mg/kg/dose four times per day, lamivudine (3TC) at 3 mg/kg/dose twice daily and lopinavir/ritonavir at 300 mg/m^2 twice daily. Ritonavir boosts the lopinavir levels.

Outcomes

Maternal Mortality

The devastating effects of TB and HIV individually and as coinfections on mothers have been presented in the introduction.

Obstetric Perinatal and Neonatal Outcomes

Earlier studies on TB in pregnancy did not show a significant effect on outcomes.[48] This has changed in recent times and the effects may be more significant in low socio-economic populations. If diagnosed and treated, the effects of tuberculosis on pregnancy and the neonate are not so serious but in populations with a low socioeconomic status tuberculosis increases the risk of abortions and premature delivery.[49] In studies from India, the outcome of pulmonary tuberculosis in 79 pregnant women compared to 316 cases matched for age and socioeconomic status revealed infants born to women with tuberculosis were significantly lighter than the controls, there was a two-fold increase in prematurity (22.8% vs 11.1%), a small size for gestational age (20.2% vs 7.9%) and a 6-fold increase in perinatal deaths (10.1% vs 1.6%). These adverse effects were more pronounced in those cases in which tuberculosis was diagnosed late in pregnancy, when adherence to anti-tuberculosis treatment was poor and in those with advanced pulmonary disease.[50] A similar study on 33 pregnant women with extrapulmonary tuberculosis, showed that disease confined to lymph nodes was not associated with adverse obstetric outcomes but that those with more serious manifestations of disease (intestinal, skeletal, meningeal, renal and endometrial) suffered similar adverse outcomes as those with pulmonary tuberculosis.[51]

In Mexico, late diagnosis and poor care resulted in a 4-fold increase in obstetric morbidity and a 9-fold increase in preterm labor.[52] In a further study from that country, the perinatal outcomes of 35 mothers with tuberculosis were compared to those of 105 healthy mothers and revealed that, in the former, the neonates were significantly smaller (2.8 vs 3.1 kg) and that the relative risks of premature delivery and perinatal death were, respectively, 2.1 and 3.1. Poor outcomes were particularly prominent in women with advanced pulmonary tuberculosis in late pregnancy.[53] In Durban, South Africa, neonates of women with tuberculosis were significantly smaller, with 49 percent having a birth weight less than 2.5 kg compared to 21.8 percent for the overall hospital deliveries.[6]

Perinatal mortality in those mothers with tuberculosis and HIV was 1.6 fold higher than for the King Edward hospital, Durban and the KwaZulu Natal region. According to the criteria of Cantwell, the overall mortality for congenital tuberculosis is 38 percent in the untreated and 22 percent in the treated.[54]

Pregnancy in women infected with HIV-1 alone tend to result in low birth weight premature babies, particularly in those with advanced HIV disease.[55,56] The outcome of pregnancy in those with both HIV disease and tuberculosis is worse but it is not entirely clear which disease has the greater bearing on adverse outcomes. In the South African study, follow-up of those infants with tuberculosis and HIV infection showed persistent or worsening clinical signs, with death occurring on an average by the age of 9 months.[41]

Management of the Pregnant Woman with TB and HIV

The pregnant woman with TB, HIV or both may present in three ways:

- The pregnant woman develops TB and is found to be HIV positive
- TB is diagnosed in a HIV infected mother who does not require ARVs for herself but therapy for the prevention of mother-to-child transmission of HIV
- Overt signs of TB may present in a HIV infected pregnant woman who has commenced ARV therapy.

Once TB is diagnosed in any of the clinical settings, prompt anti-TB therapy must be commenced in order to prevent the adverse effects in the mother, fetus and newborn. The mother must be rendered noninfectious.[50-54]

Treatment of TB in pregnant women follow the WHO recommendation and is the same as for the nonpregnant based on standard therapy for 6 months and, in coinfection with HIV prolonged to a minimum of 9 months. The first line drugs, isoniazid, rifampicin, ethambutol and pyrazinamide in standard doses, are readily absorbed from the maternal gastrointestinal tract and freely cross the placenta. The CDC recommendation

for treatment of TB in pregnancy is isoniazid (INH), rifampicin (RIF) and ethambutol daily for two months followed by INH and RIF daily or RIF and ethambutol daily for 4 months or twice weekly for 7 months, for a total of 9 months treatment in the latter group. Streptomycin should not be used due to the harmful effects on the fetus. Pyrazinamide (PZA) is not recommended as its effects on the fetus are unknown. HIV infected women should receive RIF and although the routine use of PZA in pregnancy is not recommended (in the USA), the benefits in the HIV infected woman outweigh the unknown risks to the fetus.[57,58] The recommendation for HIV positive pregnant women with pulmonary TB classified as WHO clinical stage III and IV are eligible for ARV therapy irrespective of CD4 lymphocyte counts. WHO clinical stage I and II are offered ARV therapy if the CD4 count is <200 cells/m^3.[59] The trend now is towards earlier ARV therapy and most guidelines recommend treatment when the CD4 count is <350 cells/m^3.[60]

In resource limited settings women with satisfactory CD4 counts are offered zidovudine from 28 weeks and nevirapine at the onset of labor as prophylaxis against mother-to-child transmission of HIV. In developed countries it is standard practice to offer ARVs aiming at undetectable viral load before delivery.

ARVs with concomitant TB therapy is complicated by a high pill burden, drug toxicities, drug interactions, and the immune reconstitution syndrome (IRIS). ARV therapy may exacerbate or aggravate underlying TB (reported in 20 percent patients commencing ARV therapy) IRIS is more likely to occur during the first two months of commencing ARV therapy if CD4 counts are <100 cells/m^3.[60]

In resource restricted settings, the first line regimen is of NRTIs and one non nucleoside reverse transcriptase inhibitor (NNRTI). The preferred drugs, cheaply manufactured as a fixed dose tablet taken twice a day, are stavudine (40 mg twice daily), lamivudine (300 mg daily) and nevirapine (200 mg daily for two weeks then 200 mg twice daily). Options include substitution of zidovudine for stavudine and efavirenz for nevirapine. Drug interactions between ARVs and TB therapy pose problems. RIF induces CYP450 which leads to a reduction of the plasma concentration of nevirapine by 30 percent and efavirenz by 20 to 25 percent. The clinical significance of this is not known but there are concerns that such reduced nevirapine levels may induce drug resistance and treatment failure. Increasing nevirapine dosage for compensation increases the risk for toxic effects of the drug, particularly hepatotoxicity.[61] The combination of RIF and nevirapine should be avoided particularly in pregnancy. However, it has been shown that in patients with a low CD4 count the risk of hepatotoxicity is reduced. WHO recommends abacavir or tenofir instead of nevirapine but this is an expensive option. The advantages outweigh the disadvantages. It is suggested that RIF should be used in the initial phase of TB therapy, isoniazid and ethambutol is continued and HAART with nevirapine may then be commenced. Efavirenz, much more expensive, should be avoided in pregnancy due to concern about teratogenicity. The duration of TB therapy in a HIV positive patient may have to be extended to 9 months duration and there is an ongoing risk of 'second episode' of TB.[46]

Multi Drug Resistant Tuberculosis

Drug resistant TB is increasing world wide as was noted by Edlin et al.[62] MDR TB as a cause of death in patients coinfected with TB and HIV is well recognized.[63]

Multi Drug resistant (MDR) TB defined as resistance to INH and RIF was identified among hospitalized patients with AIDS. Resistance may be primary or secondary: primary resistance occurs when an individual is infected with *Mycobacterium tuberculosis* already resistant to a particular drug; secondary resistance is when drug resistant organisms emerge as the dominant population during treatment. Risk factors for the development of MDR TB are poor adherence and compliance to therapy, inadequate assessment of response, incorrect dosage or number of dugs used as prophylaxis or treatment. Other risk factors include previous prolonged treatment of TB, contact with a patient known to have drug resistant disease, HIV infection and drug abuse. Patients suspected of MDR TB should be referred to a tuberculosis center specialized in this condition.

With the intersecting epidemics of rampant TB and the devastation of HIV, the treatment of the two conditions pose major obstacles. The side effects of drugs lead to a risk of noncompliance and nonadherence in therapies for both diseases increasing the risk for the pregnant woman and her fetus/child. The burden of pills and duration of therapies in itself poses logistical issues, MDR TB having to be treated for two years. Suspected MDR TB in a pregnant woman should be treated with INH, RIF, Ethambutol and a quinolone until culture and sensitivities are available. The newborn baby should be given high dose INH (15 mg/kg/day), ethionamide and a quinolone. Drugs contraindicated in pregnancy include the aminoglycosides, capreomycin, pyrazinimide and quinolones. Newer therapies include rifamycins, macrolides, clofazimine, amoxicillin and clavulonic acid.[64] Resistance has been documented to ciprofloxacin and oxaflacilin and these quinolones are no longer recommended.

Reports of the safety of second line drugs for MDR TB in pregnancy have appeared but very small numbers of children have been followed, 7 in the short-term and 6 children for long-term evaluations.[65] The drugs appear to have no adverse effects on the children and none had acquired TB.[65,66]

In our setting a few pregnant women have had MDR TB, so far their babies have been TB negative. WHO is in the process of developing further guidelines for TB, MDR TB and congenital TB which may change current approaches to therapy. From India guidelines have been summarized for the management of pulmonary TB, extra-pulmonary TB and TB in special circumstances.[67]

Breastfeeding or Formula Feeding

Breastfeeding is recommended by the American Academy and the Revised National Tuberculosis Control in India.[16,68] Tuberculosis is transmitted by the aerogenous route, the mother with open tuberculosis can still infect her baby if she formula feeds. However, the risk of transmission through breast milk is negligible and the baby is either on prophylaxis or treatment for TB. In the more advantaged setting, mothers can choose replacement feeding. The first line anti-TB agents are excreted in milk in very small amounts and have no adverse effects, and does not seem to predispose to the development of drug resistance. Breast milk carries a risk of transmission of HIV, however, exclusive breastfeeding reduces HIV transmission when compared to mixed feeding.[68] In addition, mixed feeding carries a risk of increasing diarrheal and respiratory infections.[69] The above is of relevance in underprivileged communities. The risks of a higher infant mortality, severe pneumonia and diarrhea by 6 months of age on formula feeding was shown in the MASHI study.[70] However, in settings where replacement feeding is feasible, affordable and safe, HIV infected women should be encouraged to exclusively formula feed. This follows the WHO recommendations.[69]

Further support for women who are HIV positive and who wish to breastfeed, comes from the studies indicating that flash heating of maternal milk inactivate HIV with about a 20 percent loss of proteins and antibodies.[71] This method has been shown in the neonatal unit at King Edward VIIIth Hospital, Durban, to be feasible and practical; some mothers are undertaking flash heating at home. The method is a simple one of expressing breast milk into a 'jam jar', closing it, placing the jar is a pot of cold water with the level of the water two finger breadths above the level of the milk in the jar, heating the milk to a rapid boil, removing the jar. The milk is allowed to cool for 10 to 15 minutes and may then be given to the baby. Milk not used immediately may be placed in the refrigerator and used at the next feed. A number of studies have shown the reduction in HIV transmission during breast feeding using different combinations of ARV therapies. A few will be quoted.

Extended ARV prophylaxis with NVP dual therapy with NVP and AZT for 14 weeks of life significantly reduced breast milk transmissions.[72] Kilewo et al showed that maternal HAART for 6 months and infant NVP for 6 months were equally efficacious in reducing postnatal transmission through breast milk at 6 months.[73]

With the access to treatment with ARVs during pregnancy, the postpartum period and of the newborn, the risks of HIV transmission through maternal breast milk is negligible resulting in more hope for improved outcomes for mothers and babies.

Stigma

Both HIV and TB are associated with stigma which has resulted in added suffering due to lack of disclosure, discrimination and criminalization to mention the commonest associations with stigma. Stigma has seriously impeded the care of patients, increased morbidities, the implementation of programs and, in some circumstances, resulted in poor adherence.[74,75]

Conclusion

The HIV/AIDS epidemic along with the increasing numbers of TB have spiraled mortality rates of women in the childbearing age. Both diseases are independent risk factors for and act synergistically for maternal mortality. The fetus and newborn are at risk of exposure to two serious infections with poor effects on the fetus and newborn. It is crucial to consider TB and HIV in every pregnant woman in high prevalence areas, to treat TB promptly and consider ARVs where relevant. A high index of suspicion is essential to diagnose TB in the newborn and to commence prophylaxis or anti-TB treatment timeously to avoid severe illness or death. Early treatment improves the prognosis for both mother and baby. Anti-TB treatment should be commenced for two weeks before commencing ARVs. Careful monitoring for drug side effects and toxicities is important. The CD4 count during pregnancy determines the ARV therapy the mother should receive, prophylaxis for mother to child prevention of transmission of HIV or ARV treatment for the mother which will prevent transmission to the fetus. There is no question that treating HIV reduces the risk of coinfections, TB and halts the progression of the disease. The side effects of ARVs is what will have to be contended with. Flash heating of HIV positive mother's milk and extended prophylaxis to mother or baby during breastfeeding will allow minimal transmission to the

infant. It is critical to halt these devastating epidemics- adequate mother to child transmission is the first step in the process, 'breaking the silence' around the TB and HIV is critical if global improvements are to be seen.

Education needs to be extended to all members of communities to include men and boys who are the fathers and the future fathers. Women still need to be educated, be literate and empowered to bargain for their own and their children's health.

Case Studies

CASE 1

The clinician has to be very vigilant for maternal TB that would alert the clinician to the possibility of the diagnosis of TB in the newborn. Clinical condition of the mother, history of pneumonia that is not improving and a low CD4 count are markers to consider the acute diagnosis.

A 29-year-old mother, a primi, delivered prematurely at home. The baby was taken to a level one hospital and then referred to a regional hospital.

Mother

She had a brief period of antenatal care during which she tested HIV positive and the syphilis serology was negative. Her CD4 count was initially not available to us and was subsequently noted to be 54 cells/m^3. She had in fact been commenced on antiretroviral therapy just before delivery. There was a delay for about a week before the mother eventually gave this information.

On day 25 postdelivery, since the baby was not responding appropriately to therapy it was decided to request a maternal chest radiograph. This revealed hilar adenopathy and pulmonary infiltrates suggestive of TB. This could be an immune reconstitution situation with TB being exacerbated within a few weeks of commencing ARVs in a patient with a very low CD4 count. There was a history of a pneumonia that the obstetricians had just begun to examine.

Baby

On admission the baby was cold and in hypovolemic shock. The baby was resuscitated and was noted to have respiratory distress. Nasal continuous positive airway pressure (nCPAP) was commenced and baby received two doses of surfactant replacement therapy. The initial chest radiograph suggested hyaline membrane disease. Baby was anemic with a HB of 9.5 mg/dl and was transfused. nCPAP was continued for 4 days, baby appeared better and the nCPAP was discontinued.

A ductal murmur was noted on day 6 and medical closure failed. In order to control the cardiac failure furosemide was given.

The chest radiograph (Fig. 3.6.1) showed deteriorating changes and since all cultures were negative second line antibiotics were commenced.

On day 9, baby had worsening respiratory distress and required to be ventilated. A decision was taken to undertake a bronchoalveolar lavage (BAL) for acute bacterial infections, respiratory viruses as well as TB and PCP. Other investigations for tuberculosis were undertaken. The BAL showed initial results of two organisms *Klebsiella pneumoniae* and *Streptoccocus pneumoniae*. Appropriate antibiotics were given. A few days later the blood culture revealed a Candida species sensitive to fluconazole and this drug was commenced.

On day 25 the maternal chest radiograph had features suggesting tuberculosis and three drug anti-TB therapy was commenced.

Laboratory Results

- The full blood count: The hemoglobin remained stable following the initial blood transfusion.
- The white cell count remained in the normal range with slight shift to lymphocyte dominance
- The platelet count remained within the normal range
- Blood culture – candida species
- The serum sodium dropped to 126 mmol/l on two occasions and this was corrected
- The serum albumin was around 20.
- The liver enzymes showed a rise in the GGT to 314 mmol/l after 10 days of anti-TB treatment, subsequently it declined without intervention.
- The BAL PCR for TB was positive.
- Chest radiograph Diffuse changes.
- Tests for TORCH syphilis and parvo virus were negative.



Fig. 3.6.1: Chest radiograph of this baby

Important Points in this Case

Mother

- Apparently unexplained preterm labor
- Pregnancy aggravates TB
- Very low CD4 count
- History of pneumonia postdelivery
- TB-possible IRIS following ARV therapy.

Baby

- Baby preterm and wasted
- Baby persistently ill
- Many organisms cultured from BAL
- Positive blood culture for Candida
- Not responding to usual therapies
- Chest radiograph nonspecific changes as in majority of cases
- Rise in GGT not unexpected.

Follow-up

- Treatment of sepsis was successful
- The ductal murmur was medically treated with Brufen
- Baby was eventually formula fed as mother was too ill to manage breastfeeding
- Initially baby was given donor milk for about 10 days
- Baby was discharged thriving and has done well on follow-up
- 6 weeks and 6 months PCRs were negative
- Family very supportive and assisted greatly with this baby

Case 2

In this case the diagnosis of TB was soon after delivery because the mother was tachypneic, wasted and was known to have a low CD4 count.

A mother aged 35-years-old, G2P1, delivered vaginally at 34 weeks gestation.

Baby weighed 1790 gm and was wasted.

Mother

She tested HIV positive in pregnancy and commenced AZT just before delivery at her local clinic. Her CD4 count was 42 cells/m^3. The syphilis serology was negative.

The mother was wasted, tachypneic and her chest radiograph was suggestive of TB. Anti-TB treatment was commenced immediately.

Baby

Initially baby had respiratory distress and was given nasal continuous positive pressure with surfactant replacement therapy. The initial chest radiograph suggested hyaline membrane disease. This treatment was discontinued on the second day. The hemoglobin was 10.1 gm /dl and baby was transfused following blood samples having been taken for causes of anemia. The white cell count wa 4.2×10^9cells, the platelet count was 107×10^9cells. Th C reactive protein was less than 5.

Soluble penicillin was prescribed. In view of th maternal history baby was investigated for TB and thre drug anti-TB therapy commenced.

The mother insisted she wished to formula feed th baby despite adequate counseling.

The chest X-ray at this stage showed non-specifi changes bilaterally.

On day 7 the baby developed abdominal (Fig. 3.6.2 distension. The abdominal X-ray revealed dilated thickened loops of bowel with features suggestin necrotizing enterocolitis. Total parenteral nutrition wa commenced. The antibiotics were changed t cefotaxime, amikacin and flagyl.

The blood cultures were negative, CSF normal electrolytes, urea and creatinine normal.

TORCH, Parvo virus results were negative.

Important Points in this Case

- Mother a late TB and baby has to receive full treatmen
- Mother clinically ill
- Baby preterm and wasted
- Baby's initial chest radiograph showed commo condition of prematurity
- Repeat chest radiograph suspicious
- Formula feeding might have been the predisposin factor for NEC, flash heated maternal milk would hav been a better option
- Baby treated very early postnatally so frank signs o chronic illness and /or TB will not be an issue



Fig. 3.6.2: Chest and abdominal radiograph of this baby

- TB microscopy and cultures of induced sputum, gastric washings and cerebrospinal fluid were negative for TB.

Follow-up

- Baby responded well to standard anti-TB therapy
- He thrived. The PCR was negative at 6 weeks and 6 months
- She breastfed the baby – flash heated her breast milk
- Family assisted mother.

Key Messages

- Consider HIV and TB in every pregnant woman
- Prompt anti-TB treatment is critical where relevant for improved perinatal outcomes
- The CD4 count must be obtained to determine the ARVs the mother is to receive
- Feeding issues have to be addressed in all settings
- Education of communities to overcome stigmatization and assist family members.

Acknowledgments

Dr T Pillay's Thesis has made a major contribution to the problem of TB coinfection in HIV infected women and newborns.

Two previous works have been published on similar lines. Chapter on tuberculosis and tuberculosis/HIV coinfection in pregnancy. Seminars in Fetal and Neonatal Medicine 2009;14:234-40.

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SECTION IV

HIV and the Adolescent

4.1

Growing Up with HIV: The Challenges and Concerns Associated with Perinatally Infected HIV-1 Positive Youth

Sunanda Gaur, Patricia Whitley Williams, Amisha Malhotra

The availability of Highly Active Antiretroviral Therapy (HAART) has resulted in a dramatic transformation in the face of Pediatric HIV. Long-term survival among perinatally infected children has become a well recognized phenomenon in high resource settings and is increasingly being recognized in resource limited settings as well. Early in the epidemic perinatal HIV infection was associated with very high mortality and morbidity, however, since the arrival of antiretroviral (ARV) therapy in the early 1990s, drug therapy guidelines have changed from the suboptimal single drug regimens to dual to potent triple-drug regimens, leading to significant improvement in outcomes. The introduction of genotypic and phenotypic resistance testing has also allowed for selection of the most effective combinations to improve clinical outcomes. These advances have led to survival of children well into adulthood while facing the day to day challenges of living with perinatally acquired HIV as a chronic illness. This chapter will discuss current data regarding survival of children with perinatal HIV, the new and emerging multifaceted challenges becoming evident as increasing numbers of children reach teenage and young adulthood and management strategies to address the unique set of issues faced by clinicians caring for these youth.

Early reports focusing on survival in pediatric HIV demonstrated high levels of mortality. In 1997, Blanche et al reported on 392 infected children enrolled in two European prospective studies of infants born to HIV infected women. Progression to US Centers for Disease Control and Prevention (CDC) group C disease or HIV related death was estimated at 20 percent during the first year of life, and 4.7 percent per year thereafter, giving a cumulative incidence of 36 percent by 6 years. The early, severe form of HIV disease occurred in 20 percent of infants, and after 6 years only 75 percent of infected children were still alive.[1] In contrast, reports from late 1990s and early 2000, started to show improving survival and decreasing morbidity. Rolando et al reported on a cohort of 129 children followed in three clinics in Southern California from 1994-2001. The use of HAART increased from 0 percent in 1994 to 93 percent in 2001, whereas the use of PCP prophylaxis decreased from 55 to 16 percent during this time period. The hospitalization rate decreased from 6.49 admissions per hundred person years in 1994 to 0.60 admissions per 100 person-years in 2001. Acquired immunodeficiency syndrome associated hospital admission rates decreased from 15.6 percent in 1994 to 0 percent in 2001. Similarly, the admission rate for patients with CDC category B disease decreased from 29.7 percent in 1994 to 5.9 percent in 2001. Logistic regression analysis showed that CD4+ cell percentage and viral load were independently associated with risk of hospitalization. Survival was significantly longer for those who received HAART.[2] McConnel et al reporting on a cohort of more than 2000 children followed in the CDC's Pediatric Spectrum of HIV Disease Study (PSD) in the USA demonstrated that ARV therapy use increased from 27 to 66 percent during 1997 to 2001 and the survival rates for the 1997 to 2001 birth cohorts were significantly better than for the 1989 to 1993 and 1994 to 1996 cohorts ($P < 0.0001$).[3] In the most recent data published from the USA, between 1993 and 2006, 3,553 US children and adolescents infected with HIV were prospectively followed. Of those children, 298 have died. Growing numbers of children with HIV began receiving HAART between 1994 and 2000, and death rates declined annually during the study period. Nearly 60 percent of all deaths in the study occurred before 1997, before the advent of HAART and the children who died were almost four times as likely to have never received HAART as those who survived. In 1994, the mortality rate for HIV infected children and youth younger than 21 years of age in the United States was 7.2 deaths per 100 person years. By 2000, that rate had plummeted to 0.8 deaths per 100 person years and remained stable through 2006.

The mean age at death for HIV infected youth in the study more than doubled from 8.9 years in 1994 to 18.2 years in 2006.[4]

Outside the USA, in other resource rich settings, similar reports have emerged. In a report of 944 children from a United Kingdom and Ireland cohort, mortality was stable before 1997 at 9.3 per 100 child years but fell to 2.0 per 100 child years in 2001-2 (P< 0.001) and progression to AIDS also dramatically declined. From 1997 onwards the proportion of children on three or four drug antiretroviral therapy increased and hospital admission rates also declined by 80 percent.[5] Judd et al from HIV Pediatric Study (CHIPS) and the National Study of HIV in Pregnancy and Childhood (NSHPC) in England and Ireland reported that the combined rate of AIDS and mortality decreased from 13.3 cases per 100 person-years before 1997 to 3.1 and 2.5 cases per 100 person-years, respectively, during 2000-2002 and 2003-2006; rates of hospital admission also declined during this interval.[6] Resino et al reporting on behalf of the Spanish Group of Pediatric HIV Infection compared the outcomes between the years 1980–1989 (pre HAART) to the years 1999-2003 when more than 60 percent were receiving HAART. The AIDS rate was >50 percent in the early years but decreased to 2 percent between 1999-2003. The mortality rates in the earlier years and later years were 16 percent and thereafter decreased to 0.5 percent respectively. The relative risk for hospitalization and duration of hospitalization also decreased significantly.[7]

In recent years, encouraging survival data, comparable to those observed in developed countries, are also being reported from resource limited countries. Rouet et al from Abidjan, Cote d'Ivoire reported a cohort of 78 children followed on HAART regimens for 4 years demonstrating a 92.3 percent survival at 6 months, 91 percent at 12 months, 88 percent at 18-36 months, and 86 percent at 42 months after start of ARV therapy.[8] Thanyawee et al reported on the results of antiretroviral treatment in 192 children with perinatal HIV followed in Thailand's National Access to Antiretroviral Program for People Living with HIV/AIDS. The mortality rate in this cohort decreased from 5.7 percent in the first 24 weeks of initiation of treatment to 0 to 0.6 percent in the subsequent 24-week intervals.[9] In Brazil, Matida et al studied the survival trends in a group of 914 children followed with perinatal HIV between 1983-1998. While half of the children died within 20 months of diagnosis in the beginning of the epidemic, 75 percent of children diagnosed in 1997 and 1998 were still alive after four years of follow up.[10] Recent developments in the care of children living with HIV in India are encouraging as well. As of May 2008, over 10,000 children are currently receiving ART, an exponential increase from 1,800 children in October 2006. A longitudinal analysis of a cohort of 295 children on ART according to NACO guidelines in Tamil Nadu indicated that the one-year survival rate was 90 percent, which was comparable to results in both resource-rich and resource-limited settings.[11]

Causes of Death and Spectrum of Disease

As children with vertically acquired HIV are surviving into their teen years the causes of death have been changing and evolving. Prior to the advent of HAART the major causes of death among children with HIV were Pneumocystis jirovecii (formerly carinii) pneumonia (PCP) and systemic bacterial infections while in the post HAART era the deaths from opportunistic infections such as PCP have declined. In a retrospective review of 58 deaths that occurred in HIV infected children followed at the New York Hospital-Program for Children with AIDS during a 7-year period from January 1990, to December, 53% of the 15 children who died in 1990 died of PCP pneumonia while none of the10 deaths were from PCP in 1996. This analysis also reported that compared with children who died in 1990, HIV infected children who died in 1996 were significantly older, more lymphopenic and more likely to have a greater number of organ system involvement. In 1996 Mycobacterium avium complex and *P. aeruginosa* became the two most important opportunistic infections causing death.[12] More recently, reporting on a US cohort of 3553 children prospectively followed between 1993 and 2006, Brady et al found that in the early years of the study, secondary infections killed more than one-third of the children, but from 2002 to 2006, that proportion fell to less than one-fourth. Over time, children and adolescents with HIV became more likely to die of kidney failure, stroke, or AIDS-induced multiple organ failure. The most common causes of death were "End-stage AIDS" (N = 48, 16%) and pneumonia (N=41, 14%). The proportion of deaths due to opportunistic infections (OIs) declined from 37 percent in 1994-1996 to 24 percent after 2000. All OI mortality declined during the study period. However, a greater decline was noted for deaths due to Mycobacterium avium complex and cryptosporidium. Deaths from "End-stage AIDS," sepsis and renal failure increased.[4]

The clinical picture of perinatally infected children surviving into their teens due to treatment with HAART regimens is different from those who did not have the benefit of treatment advances and either succumbed to HIV in early childhood or were severely compromised due to the devastating effects of HIV. The incidence of newly acquired classic OI such as PCP is on the decline while noninfectious complications of HIV are more

frequently encountered. Data from prospectively followed cohort such as the ACTG 219C cohort in the US are starting to provide some information regarding the clinical manifestations of Chronic HIV infection in these youth living with HIV. In a study of 2767 children from 2000-2004 in the US, with a mean age of 8.2 years, the incidence rates of first occurrence of bacteremia, PCP, disseminated *Mycobacterium* avium complex, lymphoid interstitial pneumonitis, systemic fungal infection, cytomegalovirus retinitis, and tuberculosis were all less than 0.50 per 100 person-years, considerably lower than that reported in pre HAART years. The four most common infections reported in this time frame were bacterial pneumonia, herpes zoster, dermatophyte infections and oral candidiasis.[13] In an analysis of 2575 HIV infected followed from 2000-2006 reported that the enrolled subjects were relatively healthy. The median age of this cohort was 9.3 years. Two thirds of these children had a CD4 percent higher than 25 percent, and more than two thirds had a viral load <10,000 copies/ml. Seventy five percent of them were receiving HAART, 15 percent were on ARV but not HAART and 10 percent were on no ARV therapy. This study tracked fifteen types of non infectious diagnoses among this cohort over the 6 year study period. The ten most common noninfectious conditions (excluding gynecologic cancers, dysplasias and pregnancy) reported were encephalopathy, pancreatitis, cardiac disorders, renal disorder, peripheral neuropathies, birth defects, idiopathic thrombocytopenic purpura, condyloma and non-AIDS cancers. Disorders such as renal complications, pancreatitis and cancers were seen most frequently in patients with viral load greater than 100,000 copies/ml whereas peripheral neuropathy was primarily seen in patients with viral loads <5000 copies/ml indicating that peripheral neuropathy was probably related to ARV therapy and good adherence. Furthermore, this study also demonstrated statistically significant decreases in the incidence rates of the first episodes of encephalopathy, pancreatitis and cardiac related conditions and a significant increase in the rate of first time pregnancies and gynecological dysplasias.[14]

These studies demonstrate that despite treatment advances, perinatally infected youth with HIV continue to develop infectious and noninfectious complications with a continually evolving clinical picture. These youth face the unique challenge of advanced antiretroviral drug resistance and the need for life long adherence with complex treatment regimens at a developmental age when medication adherence is classically poor, compounded by complex psychosocial, mental and neuro-cognitive issues, making the management of HIV disease in these teens particularly challenging. The unique challenge facing these teens must be recognized and understood in order to provide appropriate medical management. This goal is best accomplished in an adolescent oriented, comprehensive multifaceted environment utilizing a multidisciplinary team.

Reproductive Health and Perinatal HIV

As increasing numbers of perinatally infected children reach adolescence the need for health education regarding pregnancy, contraception, safe sex, and mother-to-child transmission of HIV has been highlighted by reports of sexual activity and sexually transmitted infections and pregnancy in teens with perinatal HIV. In the Pediatric Spectrum of Disease project in the US, at least 27 percent of adolescents with vertically acquired HIV infection were sexually active, and of the sexually active adolescents in the study, inconsistent condom use was common.[15] Wiener et al, in a study of 40 HIV + adolescents/young adults, found that as many as 41 percent reported being sexually active and that their knowledge about HIV transmission and safer sex practices was low.[16] Of note, in one study perinatally infected youth were less likely to be sexually active than their uninfected peers.[17] In a large US cohort (PACTG 219C), of 638 adolescent girls (age range, 13.0 to 24.7 years) studied, 174 (27.3%) were known to be sexually active by self-report, history of sexually transmitted disease, or known pregnancy. Sexually active girls were more likely to be older, of Hispanic origin, live independently, have a higher HIV RNA level and a lower CD4 percentage. Details of the contraceptive practices were not reported, however considerable proportion had reported engaging in unprotected intercourse.[18] Another study comparing contraceptive practices among HIV infected youth versus uninfected at-risk youth found that 94 percent of HIV infected vs. 89 percent of at-risk youth reported choosing a contraception method with demonstrated efficacy when used consistently. Approximately 50 percent chose partner condoms. HIV infected youth were more likely to report 100 percent partner condom use in the past 3 months (73% vs. 46%; or 3.3; 95% CI: 1.7-5.6). At-risk youth were 2.5 times more likely than HIV infected subjects to report using nothing (95% CI: 1.1-5.8).[19] A study from Uganda examining sexual practices of 732 perinatally infected youth, ages 15-17 years old demonstrated high levels of sexual activity and inconsistent condom use among these youth.[20]

Data regarding the frequency and complications of sexually transmitted infection (STI) in perinatally infected youth are emerging. In one study, 165 (94.8%) of the sexually active perinatally infected girls received a pelvic examination but only 101 (58.1%) had a documented Pap test. The rate of abnormal cervical cytology was 29.7 percent at first examination and was 47.5 percent overall among the 101 participants who had Pap smears. This

rate was more than double the 11.5 percent found in a previous study among HIV-free university students. The majority of abnormalities were low-grade squamous intraepithelial lesions, followed by atypical cells of undetermined significance, and high-grade lesions at the first examination. Many cervical abnormalities persisted despite intervention (nine of 21 cleared after intervention, six of 14 untreated lesions cleared). This high proportion of abnormal cervical cytology reported in this study could be because of increased susceptibility and persistence of human papillomavirus and other genital infections in these girls, as has been demonstrated in HIV infected women. In this study Condylomata and trichomoniasis were the most frequent genital infections reported.[18] These data support the American College of Obstetricians and Gynecologists recommendation of a first ob-gyn visit for girls between ages 13-16 and the need for yearly screening Pap smears in this high risk population.[21]

Limited data from studies in HIV infected women have demonstrated that several PI and NNRTI medications interact with oral contraceptives leading to decreases in ethinyl estradiol or increase in estradiol or norethindrone levels, thus raising the possibility of reduced effectiveness of some oral contraceptives and increased chances of side effect from increased levels of estrogen or progesterone. One study has reported that the efficacy of progesterone only injectible contraceptive depot methoxyprogesterone acetate (DMPA) was not affected among women receiving nelfinavir, efavirenz, or nevirapine based treatment regimens during a three month follow up period.[22]

Pregnancies in vertically infected adolescents have been reported from the United States,[18,23,24] Puerto Rico,[25] India[26] and Europe.[27,28] Perinatally infected women who have been able to survive to reproductive age and conceive frequently have a history of sequential monotherapies that changed as drugs gradually became available to pediatric patients. As a result, they may have acquired substantial drug resistance, which would require a more complex drug regimen. Since these women are also younger, they are at higher risk for acquisition of other sexually transmitted diseases during pregnancy, and they require monitoring and testing as well as active case management.

In the US 219C cohort, of the 638 perinatally infected girls older than 13 years, thirty-eight girls became pregnant giving a first pregnancy rate of 18.8/1000 person years which is lower than the pregnancy rate among presumed non HIV infected teens in the US in 1999 (86.7/1000). For girls aged between 15 to 19 years, the first time pregnancy rate was 33.5 per 1000 person-years. Lower pregnancy rate has also been reported in HIV infected US women; however, no biological association between female infertility and HIV infection has been substantiated.[29,30] All girls received antiretroviral therapy during pregnancy. Thirty-two of these pregnancies resulted in live births. One infant was HIV infected, 29 were uninfected, and 2 had unknown infection status, for a rate of mother-to-child transmission of HIV of 3.3 percent (95% CI=0.1, 18.6).[18] In a series of pregnancies in 9 patients with perinatal HIV from the United Kingdom and Ireland's National Study of HIV in Pregnancy and Childhood and the European Collaborative Study, 11 pregnancies were reported. Nine pregnancies resulted in live births while two were terminated. In all but two of the 11 pregnancies, the women were receiving HAART at conception, and all were heavily pretreated with ARV. The median CD4 cell count closest to delivery/termination was 190 cells/ml (range 18–642).The median HIV RNA viral load in the eight pregnancies with detectable levels (>50 copies/ml) close to delivery/termination was 361 copies/ml (range 59–6600). Eight of the nine infants were either proven or presumed uninfected and one had indeterminate status at the time of publication resulting in a very low transmission rate in this very small study population. Although this corresponds to a 0 percent mother-to-child transmission rate, the 95 percent confidence limit would be 36.9 percent. Two infants had low birth weight and two had congenital abnormalities: partial malrotation of the gut; ventricular septal defect and patent foramen ovale.[27] Similarly in a cohort of 26 perinatally infected adolescents from Manipur, India, all delivered live born infants, of these, one was a preterm delivery (35.2 weeks). There was no Intrauterine fetal demise, Intrauterine growth retardation, spontaneous miscarriages, infant or maternal deaths.[26]

In a brief review from Puerto Rico focused of 8 perinatally HIV infected young women with 5 first pregnancies resulting in live births, of the 5 pregnant women, 4 were treated with combination antiretroviral therapy during pregnancy, and no mother-to-child transmissions occurred.[25]

These studies underscore the importance of considering sexual practices in young women when choosing antiretroviral regimens such as Efavirenz that are known to cause fetal adverse effects. Additionally, discussions regarding safe sex practices, reproductive plans, use of contraception and screening for sexually transmitted infections and pregnancy should be incorporated into routing clinical care. Full understanding of the outcomes in these pregnancies will emerge as more women are followed and reported. Thus far, based on data from small series of patients there does not seem to be an increase in adverse outcomes of pregnancy in perinatally infected women.

Treatment and Management of the Perinatally-infected HIV Youth

Management of pediatric HIV disease in the United States has evolved since it was first discovered in the 1980s. Prior to the availability of antiretroviral agents, children diagnosed with perinatally-acquired HIV were managed with a focus on opportunistic infection treatment and prevention and palliative care. These children faced a bleak prospect for health and survival until the arrival of antiretroviral medications in the late 1980s. Zidovudine (AZT) was the first antiretroviral agent to be used in adults and children with HIV type 1 infection which showed promise. Adults infected with HIV who were given AZT lived longer than those who did not.[31] By the 1990s, newer classes of antiretroviral agents became available, and AZT monotherapy was replaced by dual and triple combination based regimens involving both nucleoside reverse transcriptase inhibitors, non-nucleotide reverse transcriptase inhibitors and protease inhibitors which target the reverse transcriptase (RT) and protease (PR) gene respectively, on the HIV-1 viral genome, to inhibit replication.

Currently, highly active antiretroviral therapy (HAART), consisting of three or more antiretroviral combination regimens, which include at least 2 classes of drugs, has successfully become the mainstay of treating HIV infected children and adolescents. Children on appropriate HAART therapy have significantly lower mortality and improved survival and quality of life.[32-34] The use of HAART has shown an improvement in the clinical, virological and immunological outcomes of infected children where these children are living into and beyond adolescence.[35] The average age of perinatally infected HIV-positive children living in the United States today is 15 years. Older children and adolescents now make up the largest percentage of HIV infected children cared for at US sites.[36] Since children are now living with HIV into adulthood, caretakers are faced with newer challenges in managing these patients and their medications. Many of these challenges include monitoring their medical therapy as they grow older and management of treatment failures which may be a result of many factors including drug resistance and adherence issues.

Clinical Management of Children on Antiretroviral Therapy

Most perinatally infected adolescents have generally had a long clinical course and extensive antiretroviral treatment history with exposure to a variety of antiretroviral medications. Although children can remain on a stable antiretroviral regimen for years, routine assessment of the medication regimen is necessary. Regular monitoring of the patient's viral load and CD4 count is a useful measure of regimen effectiveness. Guidelines in the United States recommend that children and adolescents on HAART be monitored every 3 to 4 months for viral load quantification of HIV RNA and CD4 counts to assess efficacy of the ongoing medical regimen and help determine treatment failure.[37] Treatment failure is categorized into virologic, immunologic and clinical failure.

Virologic failure is defined as an incomplete response to therapy measured by HIV viral load or a rebound in viral load after achieving virologic suppression. Incomplete viral response to therapy is defined as a $<1.0 \log_{10}$ decrease in HIV RNA copy number from baseline after 8 to 12 weeks of treatment, HIV RNA >400 copies/ml after 6 months of treatment and detectable levels of HIV RNA after 12 months of treatment with antiretroviral medication.[37] Viral rebound is defined as repeat detection of plasma HIV RNA on ultrasensitive PCR assays in children and adolescents with previous undetectable plasma viral loads.

Immunologic failure is assessed by evaluating a patient's plasma CD4 T cell count. Adolescents and adults have a normal CD4 count of greater than 200 cells. Immunologic failure can be defined as a failure to achieve and maintain an adequate CD4 T cell response despite virologic suppression. There is no specific definition for immunologic failure, although some studies have focused on patients who fail to increase CD4 T cell counts above a specific threshold (e.g. >350 or 500 cells/mm^3) over a specific period of time (e.g. 4-7 years). Others have focused on an inability to increase CD4 T cell counts above pre-therapy levels and can be defined as a sustained decline of 5 percentage points in CD4 percentage below pretherapy baseline.[37] The proportion of patients experiencing immunologic failure depends on how failure is defined, the observation period, and the CD4 T cell count when treatment was started.

Clinical failure is defined as the occurrence of new opportunistic infections and/or clinical disease progression despite ongoing use of HAART for several months. This requires immediate evaluation of the clinical findings in the context of immunologic and virologic responses to therapy. Although clinical events occurring in the first several months after the initiation of a new antiretroviral regimen should not necessarily be construed as antiretroviral failure, the continued occurrence of clinical disease progression requires strong consideration that the current regimen is failing.

In general, an effective antiretroviral regimen should result in virologic suppression with resulting immune restoration and prevention of HIV-related illnesses and

an ineffective antiretroviral regimen fails to achieve virologic suppression and results in immunologic and clinical failure. However, discordant responses to antiretroviral therapy can occur with a successful response in one domain and failure in the others.

Some patients who are maintained on antiretroviral therapy may exhibit immunologic and clinical benefit despite detectable viral replication for up to 3 years.[38,39] The proposed mechanism for immunologic and clinical benefit without complete virologic suppression is the maintenance of a lower viral load or the selection for HIV strains harboring drug-resistance mutations that impair viral replication or virulence. Another possible explanation is that these patients may have host genetic and/or virologic characteristics that allow them to be either 'slow progressors' or 'long-term nonprogressors' without therapy.[40]

Poor immunologic response despite virologic suppression can occur in the context of adequate or poor clinical response. The first consideration is to exclude laboratory error in CD4 or viral load measurement and to ensure that CD4 values are interpreted correctly. Also, in patients with baseline severe immunosuppression, it is common to achieve virologic suppression weeks to months before achieving immunologic recovery, resulting in transient early-treatment period of persistent immunosuppression during which additional clinical disease progression can occur.[41,42] However, when HAART is initiated in children with severe immune compromise, complete immune reconstitution is difficult to achieve.[43] Certain antiretroviral regimens can be associated with a blunted CD4 response, i.e. adults regimens with zidovudine can also impair the rise in CD4 counts, not percentage, perhaps due to its myelosuppressive effect.[44] Several other drugs and conditions can also independently affect CD4 counts (corticosteroids, chemotherapy agents, hepatitis C, tuberculosis, malnutrition and malignancy).

Evaluation of patients with antiretroviral treatment failure consists of assessing three main concerns:

1. Adherence.
2. Pharmacokinetics.
3. Drug resistance.

Adherence

When treatment failure is observed, adherence to the regimen can be a major contributor and should be assessed since medication adherence is fundamental to successful antiretroviral therapy. Poor virologic response or widely fluctuating viral loads can be an indication of poor adherence, especially in the presence of susceptible virus. Studies have shown that even small lapses in adherence can lead to antiretroviral treatment failure.[45,46] Therefore, adherence should be addressed at each medical visit for all children receiving antiretroviral therapy and can be influenced by a large number of factors related to the drugs themselves as well as social and psychological issues of the adolescent and family and their health beliefs.

It is important to review and assess whether adherence problems are related to drug formulation, pill burden, drug dose timing and frequency, dietary restrictions or drug side effects and to determine what changes would be needed for better adherence by the patient and the patient's caretakers. Regular monitoring is the key to early identification of any problems that may arise.

Adherence to HIV medications in adolescents can be challenging and is difficult to assess. Denial, fear and the stigma of HIV are very common in these young patients, which can lead to refusal to initiate or adhere to the antiretroviral regimen. Pill burden and lifestyle issues for teens can also be a barrier to complete adherence. Some adolescents have poor growth and development as a result of their HIV infection and may also suffer from low self-esteem. Many young teens have unstructured and chaotic lifestyles with concomitant mental illness, problems with substance abuse and often have difficulty coping with their illness due to a lack of familial and social support. Adolescents with more advanced HIV disease have been found to be less adherent to their regimens and failure to maintain adherence has been associated with poor school attendance, younger age, depression and the use of alcohol or substance abuse.[47]

Adherence to complex antiretroviral regimens is very difficult at a time of life when adolescents do not want to be different from their peers. Clinicians can help improve adherence with certain strategies. Building and fostering a trusting relationship is very helpful in order to maintain open communications between the patient, the family and healthcare providers so concerns regarding adherence are addressed at the earliest. In addition, educating the patient and the family about adherence should begin before the start of antiretroviral therapy and should include a discussion regarding the goals of treatment and plans for supporting and maintaining adherence. Also, the choice of medications used in the regimen can impact adherence. To the extent possible, regimens should be simplified with respect to the number of pills as well as frequency of therapy and should be chosen to minimize drug interactions and side effects. The major rationales behind regimen simplification are to improve the patient's quality of life, improve medication adherence, avoid long-term toxicities, and reduce the risk of virologic failure.[48]

The availability of recently approved agents that have activity against drug-resistant virus and that are easier to

take without sacrificing antiviral activity may be used in this population, however, resistance testing to check susceptibility of these medications is important prior to initiation. Unlike antiretroviral agents developed earlier in the HIV epidemic, many antiretroviral medications that have been approved in recent years have sufficiently long half-lives to allow for once daily dosing, and most also do not have dietary restrictions.

It is important for clinicians to realize that nonadherence is a common problem and it can be difficult for patients to share information about missed doses or difficulties adhering to treatment. Also, adherence can change over time; a patient who was able to adhere to treatment upon initiation may not be able to maintain adherence over time. Therefore, regular monitoring is the key to early identification of problems and can reinforce the importance of taking medications as prescribed. A nonjudgemental attitude and trusting relationship can foster open communication and may facilitate assessment regarding adherence.

Drug Pharmacokinetics

In addition to poor adherence, inadequate drug exposure can result in treatment failure.[49] Children require higher weight-based dosing of antiretroviral drugs compared to adults because of developmental differences in absorption, body composition, and metabolic activity.[50] The appropriate dosing of ARV medications in adolescents is complex and depends on multiple factors, including developmental changes throughout puberty. However, very few studies have investigated the pharmacokinetics and pharmacodynamics of ARV agents in adolescents and young adults as well as the long-term effects on puberty or combined effects of ARVs with other drugs and psychotropic agents. Other causes of subtherapeutic drug levels may include impaired absorption because of gastrointestinal symptoms, such as vomiting or diarrhea, or failure to adjust dosing as the teen grows. Certain medications have food/fasting requirements which need to be reviewed with the patient and caregiver since absorption of these medications can be affected by the child's diet. In addition, some drugs can also alter the metabolism of antiretroviral medications, so all medications, including herbal supplements and over-the-counter medications, need to be reviewed to evaluate whether they are contributing to the poor treatment response. Studies have also shown that genetic polymorphisms may also influence pharmacokinetics and therapeutic responses for some antiretroviral medications.[51]

Adolescent providers are often faced with the dilemma of choosing a dosing regimen that falls between pediatric weight and surface based dosing criteria and adult fixed dose guidelines. Current US guidelines recommend using Tanner stages of puberty to help guide dosing regimens in this population: for children in early puberty (Tanner stages I and II) US guidelines recommend using pediatric schedules, whereas for adolescents in their growth spurt (Tanner stages III and IV) either adult or pediatric dosing schedules are recommended with careful monitoring for toxicity and efficacy of medications.[37] Adult dosing guidelines are recommended for Tanner stage V teens.[52] World Health Organization guidelines extend pediatric dosing to Tanner stage III and recommend adult dosing regimens for Tanner stages IV and V.[53] The continued use of higher pediatric dosing during adolescence can result in increased and potentially toxic drug exposure, whereas early introduction of lower adult doses can lead to suboptimal exposure and development of drug resistance and subsequent virologic failure.[54]

Drug Resistance

Antiviral drug resistance produced by drug-associated mutations in specific regions of the HIV genome is recognized as one of the major problems affecting treatment of HIV infection. The goal of antiretroviral therapy is to suppress HIV replication as much as possible in order to reduce plasma HIV RNA to below the limit of detection using the most sensitive assays available. HIV has the ability to mutate easily, in large part due to the error rate of the reverse transcriptase enzyme. HIV replicates at a fast rate with the generation of 10^9 to 10^{10} virions per day. This coupled with the high mutation rate of approximately 3×10^{-5} per nucleotide base per cycle results in a high mutation rate with errors occurring during replication.[55] However, alterations in HIV RNA occurring in the presence of antiretroviral drugs, select for HIV strains with mutations that confer resistance to the presenting drug. So, although combination HAART regimens increase selective pressure against viruses, they also induce the development of drug-resistant mutations.

Numerous adult studies show an association between multiple mutations and multidrug resistance in HIV isolates but resistance data in perinatally-infected HIV positive children and adolescents is lacking.[56,57] Drug resistance acquired during antiretroviral therapy is much more common than transmitted drug resistance.

For example, drug-resistant virus has been identified in 6-16 percent of antiretroviral-naïve adults and 18 percent of horizontally infected adolescents with recent infection in United States and Europe.[58-60] However, in a recent 10-year adult longitudinal study from the Swiss HIV Cohort Study, the prevalence of drug-resistant virus among antiretroviral therapy exposed patients was estimated to be 50–60 percent in 1999 and decreased to 39–53 percent in 2006.[61] The prevalence of triple drug-resistant virus remained stable at 5 percent. These lower numbers are likely to be attributable to the improving efficacy of treatment.

Data are limited in perinatally infected adolescents although infants born to mothers with HIV infection are known to carry drug mutations in their wild type HIV virus and the prevalence has increased in the last decade. In a study in New York State, genotypic drug resistance was identified in 12 percent of 91 HIV infected infants born from 1998-1999 and 19 percent of 42 infants born from 2000-2001.[62,63] History of maternal and infant antiretroviral prophylaxis was not significantly associated with the detection of resistance in the infant.

Smaller studies in children have shown the presence of antiretroviral mutations in both treated and untreated HIV infected children and several studies have shown that the failure of ARV therapy and clinical disease progression in infected children and adolescents on ARV therapy is associated with a high frequency of mutations in the RT and PR gene of the HIV genome.[64-66] Different classes of antiretroviral medications exert their effect on different areas of the HIV genome and prolonged exposure to antiretroviral medication and/or suboptimal exposure to antiretroviral medications can lead to HIV mutagenesis.

Drug Resistance and Resistance Testing

Currently in the United States, there are more than 20 approved antiretroviral drugs in 6 classes with which to design combination regimens from. These 6 classes include the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs), CCR5 antagonists, and integrase strand transfer inhibitors (INSTI). However, not all medications are approved for children and adolescents or even have dosage indications for this group. Each class of medications targets specific sites in the HIV reproductive cycle to inhibit entry into host cells or HIV replication.

Most perinatally infected adolescent children are heavily drug-experienced and therefore very likely to carry mutations in their HIV RNA. Therefore it is important to perform drug resistance testing in this group prior to changing therapy for treatment failure. Both genotypic assays and phenotypic assays are used to assess the presence of virus that is resistant to inhibitors of HIV reverse transcriptase (RT) and protease (PR).

Genotypic assays for PR and RT inhibitors are based on PCR amplification and analysis of the RT and PR coding sequences present in HIV RNA. Genotypic assays can detect resistance-associated mutations in plasma samples containing approximately ≥ 1,000 copies/mL of HIV RNA.[37] Interpretation of test results requires knowledge of the mutations selected by different antiretroviral drugs and the potential for cross-resistance to other drugs within the same class as conferred by some mutations. The significance of each mutation is variable: in certain cases, the presence of a single mutation is sufficient to confer high-level resistance to a particular antiretroviral drug or class of drugs, as seen with the presence of the K103N mutation and the NNRTIs, neviripine and efavirenz.

In some cases multiple mutations are required to confer resistance as seen with PIs. Drug resistance to most PIs requires multiple mutations in the HIV protease gene which seldom develop after early virologic failure, especially when ritonivir boosting is used. The PI, ritonivir, acts as a potent inhibitor of the cytochrome P450 3A4 isoenzyme and inhibits metabolism of other PIs. It can be used as a 'pharmacokinetic booster' when administered in low doses with a second PI since it prolongs the 2nd PI's half-life by increasing drug exposure.[52]

Other mutations may confer resistance, however, clinical benefit from the antiretroviral may still remain as seen with the NRTI, lamivudine, and the M184V reverse transcriptase mutation. In still other cases, the mutation may have little or no direct effect on resistance individually, but in combination with other mutations may show decreased (or increased) susceptibility to an antiretroviral agent or show no effect at all. Given the complexity of interpretation of genotypic resistance it is recommended that clinicians confer with a specialist in pediatric HIV infection for assistance in interpretation.

Phenotypic assays provide a more direct assessment of the impact of acquired mutations. Phenotypic assays involve PCR amplification of specific portions of the HIV RNA genome from the patient and insertion of the amplified patient sequences into a laboratory strain of HIV to form a recombinant virus. Replication of this recombinant virus occurs at different drug concentrations to calculate the drug concentration that inhibits viral replication by 50 percent. This individualized technique is helpful in assessing the efficacy of a particular antiretroviral medication, but is more costly than genotypic assays.

With the advent of newer classes of drugs including CCR5 co-receptor antagonists, newer assays to help detect resistance to these drugs have also been developed. These trophism assays involve the generation of patient-derived recombinant HIV viruses to help detect the usage of another co-receptor CXCR5, which would make the use of CCR5 inhibitor-based regimens less viable.

Limitations of resistance assays include lack of uniform quality assurance testing and high cost. Also, individuals who harbor low levels of drug-resistant mutant HIV viruses may elude detection by these current assays. Resistance testing is most valuable when performed before or within 4 weeks of discontinuing antiretroviral medication since loss of detectable resistance and

reversion to predominantly wild-type virus often occurs in the first 4 to 6 weeks after antiretroviral therapy is stopped.[67]

Although the response to antiretroviral therapy in children and adolescents is not always predicted by the results of resistance testing, adult clinical trials have demonstrated a benefit of resistance testing when used in combination with specialists in HIV care to help improve virologic outcomes. However, poor adherence should be suspected when no evidence of resistance is identified to a failing regimen.

Choosing an Effective Antiretroviral Regimen

When deciding to change a patient's antiretroviral regimen, the clinician should assess whether this change can achieve better virologic control than the current regimen. Also, the urgency of establishing viral suppression depends on the clinical and immunologic status of the adolescent and a change in antiretroviral therapy may be critical to prevent immunologic and clinical disease progression. Although complete virologic suppression with undetectable viral load is the goal, such low level of viral suppression may not be achievable in the perinatally infected adolescent and clinical benefit may be observed with decreased viral loads that are not in the undetectable range.[68] On the other hand, failure to maximally suppress plasma viral load is associated with an increased probability of acquiring resistant mutations and further limiting treatment options.[69] In addition, drug toxicities and possible side effects need also to be reviewed with the patient to help ensure maximal benefit and adherence.

Since most perinatally infected HIV-positive adolescents are drug-experienced, the approach to changing their failing regimen includes testing for resistant mutations that may be responsible for their treatment failure. If no viral resistance is found, it is very likely that the individual is not adherent to his or her regimen. Other factors such as poor drug absorption, incorrect dosing and drug interactions need to be excluded as well. It is important to administer resistance testing assays to the patient while he or she is receiving antiretroviral medication or within 4 weeks of discontinuing the medications since drug resistant strains can revert to wild-type virus and resistant assays may then fail to detect drug resistant viral strains.

If the patient is found to have viral resistance to the current regimen then the goal is to start a new regimen in order to fully suppress and sustain undetectable plasma viral loads and prevent the emergence of virus with additional resistance mutations. This regimen should include at least two and preferably three fully active agents and usually requires the use of new drug classes (Table 4.1.1). Substitution or addition of a single drug to a failing regimen should be avoided because it is unlikely to

Table 4.1.1: Options for regimens following failure of previous antiretroviral regimen with evidence for viral resistance to therapy with goal of virologic suppression*

Prior Regimen	*Recommended Change*
2 NRTIs + NNRTI	• 2 NRTIs (based on resistance testing) and PI
2 NRTIs + PI	• 2 NRTIs (based on resistance testing) + NNRTI • 2 NRTIs (based on resistance testing) + alternate PI (with low dose ritonavir boosting, based on resistance testing) • NRTI(s) (based on resistance testing) + NNRTI + alternate PI (with low dose ritonavir boosting, based on resistance testing)
3 NRTIs	• 2 NRTIs (based on resistance testing) + [NNRTI *or* PI] • NRTI (s) (based on resistance testing) + [NNRTI + PI]
Failed regimens including NRTI, NNRTI, PI	• >1 NRTI (based on resistance testing) + newer PI (with low dose ritonavir boosting, based on resistance testing) • >1 NRTI + dual boosted PI (LPV/r +SQV, LPV/r + ATV) # *Consider adding one or more of: fusion inhibitor, etravirine* ∞ *or an integrase inhibitor* • NRTI(s) + ritonivir-boosted, potent PI (based on resistance testing)+ etravirine ∞ • NRTI(s) + ritonivir boosted, potent PI (based on resistance testing) + fusion inhibitor and/or chemokine coreceptor antagonist and/or integrase inhibitor • If patient refuses PI and/or ritonavir boosting: NRTI(s) + fusion inhibitor and/or chemokine coreceptor antagonist and/or integrase inhibitor

LPV/r = ritonavir-boosted lopinavir; SQV = saquinavir; ATV = atazanavir

∞ *etravirine:* NNRTI class medication with *in vitro* activity against viral strains with mutations that confer resistance to other NNRTIs.

*Antiretroviral regimens should be chosen based on treatment history and drug resistance testing to optimize antiretroviral drug effectiveness in the new regimen. Regimens should contain two, but preferably three, fully active drugs for sustained viral suppression.

Adapted from "Guidelines for the use of Antiretroviral agents in Pediatric HIV infection." February 23, 2009.

achieve and sustain an undetectable plasma viral load and frequently results in additional drug resistance.[37] The choice of agents should be based on results of resistance testing, history of previous regimens, potential drug side effect/ toxicity profile. The availability of multiple new antiretroviral drugs and new classes of drugs makes complete viral suppression achievable for adolescent patients, however adherence to therapy and compliance need to be addressed and efforts should be made to address any barriers if they exist. In cases where poor adherence and compliance are a continuous problem, some physicians elect to continue treatment with the non-suppressive regimen which may provide some clinical and immunologic benefit while preserving future antiretroviral options.

In patients with extensive drug resistance such that two or more fully active antiretroviral agents cannot be identified, the goal is to preserve immunologic function and prevent clinical disease progression. There is no consensus to optimal management of these patients. It may be reasonable to observe these patients on the same regimen while awaiting future options. Adult studies suggest that there may be ongoing clinical and immunologic benefit if the HIV viral load can be maintained below 20,000 copies/ml.[70,71] Smaller adult studies show a clinical benefit of remaining on antiretroviral therapy despite no reduction in viral load.[72] Although, adding a single fully active ARV to a new regimen is not routinely advised, since it can cause rapid development of mutations, this approach may be considered in the patient with poor immunologic function, high-risk of disease progression, and limited drug options. Transient improvement of viral load and CD4 T cell count may halt or slow clinical disease progression. In this scenario, it may be reasonable to use investigational agents or agents approved for adults as an additional drug in the new regimen. Weighing the risks and benefits of using a single active and/or investigational antiretroviral agent in this population is complicated and consultation with an HIV specialist is advised. Discontinuing or interrupting all antiretrovirals in patients with poor immunologic function and high risk of disease progression should be discouraged, since this approach will result in increased viral load burden, further decline of immunologic function and continued disease progression.

In management of patients with advanced disease and extensive resistance, quality of life must also be considered and the burden of continuing a failing regimen should be addressed. Any decision to continue, discontinue or change therapy should be made in collaboration with the patient, his/her caretakers and the healthcare providers and should reflect the patient and their caretakers' beliefs and the goals for care.

Long-Term Complications

As perinatally HIV infected children are surviving into their adolescent and young adulthood years as a result of the availability of HAART, long-term complications including metabolic alterations, renal disease and bone disease are being reported putting them at risk for significant illnesses developing later in life.

Renal Disease

The incidence of renal disease in HIV infected children has been reported to be 2-5 percent.[73] Mortality in HIV infected children due to renal failure was reported to have increased from less than 1 to 5 percent.[74] The most commonly recognized type of chronic kidney disease (CKD) in HIV infected patients is HIV-associated nephropathy (HIVAN).[73] This entity is characterized by its histologic findings which are consistent with a collapsing form of focal glomerulosclerosis (FSGS). Children present with the clinical picture of nephrotic syndrome (i.e. proteinuria, edema and hypoalbuminemia). Renal ultrasonography in HIVAN may show large echogenic kidneys, however may also be completely normal.

An analysis of a US Registry revealed that while children with HIVAN have a better prognosis than adults with HIVAN, there was only a 54 percent survival at 36 months after diagnosis.[75] Therefore it is important to identify renal abnormalities in these children as early as possible. In a large prospective cohort study, the Pediatric AIDS Clinical Trials Group (PACTG) Study 219/219C, 22 percent of 2102 HIV infected children followed for over 30 months were found to have at least one persistent renal laboratory abnormality (elevated serum creatinine or proteinuria measured by dipstick).[76] Longer survival, Black and Hispanic ethnicity, as well as exposure to antiretrovirals, especially tenofovir and indinavir, were identified as risk factors.[76] Monitoring for proteinuria, hematuria, elevated serum creatinine or blood urea nitrogen, and hypertension in HIV infected children should be part of routine care.

Bone Disease

Bone mineral density (BMD) as measured by dual X-ray absorptiometry (DEXA) has been studied in HIV infected children and adolescents. Prior studies have documented decreased BMD in HIV infected children making them at potential risk for future fractures.[77-83] Factors contributing to alteration in bone metabolism include HIV infection, host immunity, and initiation of antiretroviral therapy as well as other factors not clearly

understood. A prior longitudinal study of a small number of HIV infected children being treated with tenofovir disoproxil fumarate demonstrated a significant decrease in BMD over a 48 week period.[84] A one year longitudinal study reported a lower baseline BMD in HIV infected patients compared to healthy controls.[81] Increased markers suggesting a high rate of bone turnover were not affected by antiretroviral therapy.[81] There remains a concern that children may not attain adequate peak bone mass. Future studies are needed to elucidate further the mechanisms which control bone resorption in HIV infected children, as well as the role of chronic cytokine production and the impact of the various antiretroviral therapies on BMD.

Metabolic Abnormalities

With the widespread use of protease inhibitor (PI)-containing HAART regimens, metabolic abnormalities such as lipodystrophy (fat redistribution syndrome), dyslipidemia (hypercholesterolemia and hypertriglyceridemia) and insulin resistance and have been reported in adults[85,86] and now in children.[87,88] As perinatally infected children are now surviving into young adulthood, they will be at risk for adverse cardiovascular outcomes in their middle aged years.

Lipodystrophy syndrome refers to clinical features associated with fat redistribution and can result in lipoatrophy or lipohypertrophy or a mixed picture of both. Fat loss occurs in the face, extremities and buttocks. Lipohypertrophy presents as increased fat accumulation in the breasts, dorsocervical area ("buffalo hump") and abdomen (central obesity). A review of prior international studies in children reported that the prevalence of lipodystrophy were 10 to 43 percent.[87] A longitudinal study of perinatal HIV transmission and natural history study of perinatally infected children reported a prevalence of 5.6 percent.[88] The body composition changes of lipodystrophy which can be quite disfiguring tend to occur in postpubertal children. Children in this age group are very much concerned about their body image. When the patients realize that the body changes can be attributed to the medications, some stop taking their medications. Maintaining medication compliance then becomes a challenge for the patient, the caretaker and the provider. These changes persist even after discontinuation or changing of the antiretroviral regimen. Some patients experience an initial reduction in the dorsocervical fat, however it is common for the reaccumulation of this fat. Diet and exercise generally do not address the problem of lipodystrophy although some patients may experience mild weight loss. The duration of persistence of the lipodystrophy syndrome in children is not completely known but has been observed to last for years.

Risk factors have not been completely identified but include exposure to and duration of nucleoside reverse transcriptase inhibitors (most often stavudine), and in combination with protease inhibitors (ritonavir). Other factors included are ethnicity, age and disease markers (CD4 and viral load).[85,89] Lipodystrophy is thought to be due to the effect of antiretrovirals alone and in combination on lipid metabolism, adipocytes and fat distribution, however further investigation is warranted. While several pathogenetic pathways have been proposed to understand why lipodystrophy occurs, the exact mechanisms have yet to be elucidated but probably involve complex and integrated interactions between medications, infection and host immunity and genetics.[90]

In prior studies the prevalences of hyper cholesterolemia ranged from 10 to 68 percent and hypertriglyceridemia from 13 to 67 percent.[87,88] Undetectable viral load, exposure to protease inhibitor containing regimens and severe immunosuppression were identified as independent risk factors for hypercholesterolemia.[88] On the other hand, hypertrigliceridemia was associated with the use of protease inhibitors and having a body mass index of >90th percentile for age and gender. It is important that lipid levels be monitored in children on PI-containing. Diet and exercise are recommended as the initial intervention in children with hyperlipidemia, however, lipid-lowering agents should be considered in children who fail to respond.

Glucose metabolism disorders, including impaired glucose tolerance, impaired fasting glucose and diabetes mellitus have been reported in HIV infected children.[91,92] Again the exact mechanisms of insulin resistance are not well understood. A cross sectional study compared fasting glucose and insulin levels and 2-hour oral glucose tolerance tests in heavily HAART-experienced HIV infected youth ages 7 to 24 years of age to controls.[92] Although there was no detectable difference in fasting glucose levels between the groups, heavily PI-exposed HIV infected children had higher fasting insulin as well as 2 hours glucose and insulin levels compared to controls. The differences in fasting insulin levels were statistically significant when compared to controls for HIV infected children regardless of PI exposure. The fasting and 2-hour elevated glucose levels did not meet the diagnostic criteria for diabetes.

The benefit of the use of a PI-containing HAART regimen in children over many years in order to achieve viral suppression versus the risk for the early onset of atherosclerotic heart disease will need to be re-evaluated as more information becomes available about the metabolic complications in treated HIV infected youth. Given the well known risk factors for coronary artery disease— obesity and hyperlipidemia – HIV infected youth are at risk. Patient and family education about healthy lifestyles—nutrition, exercise, and smoking cessation as well

as coping mechanisms to alleviate stress should be incorporated into the medical visits. Individual/family counseling and peer support groups may also help the youth to cope with their chronic illness and its complications.

Cognitive Disorders

Primary HIV infection of the central nervous system (CNS) is well known and in the pre-antiretroviral therapy (ART) era, a wide spectrum of neurocognitive and developmental delay were observed in HIV infected children. In resource challenged countries where large numbers of infected children may not have access to ART, these neurologic abnormalities persist. Neurologic impairment may also be a result of CNS opportunistic infections such as TB or Cryptococcal meningitis or CNS Toxoplasmosis. Socioeconomic factors, prenatal illicit drug exposure and CNS complications associated with very low birth weight such as intraventricular hemorrhage, cerebral infarct and severe ischemia also play a role worldwide in the development of neurocognitive disorders.

Studies have reported the effects of HIV on child development include cognitive, motor and adaptive impairment.[93-95] The prevalence of cognitive delay ranges from 8 to more than 60 percent. This wide variation is due to the different testing modalities used to assess development and cognitive function, different populations, variations in socioeconomic backgrounds of the children as well as variations in access and exposure to HAART. Developmental delays include impairment in language skills, motor skills, executive cognitive function, deficits, integrative skills, and impulsive behaviors.

Both poor socioeconomic environment and severe immunosuppression and poorly controlled HIV infection correlate with increased neurocognitive impairment. As the use of HAART evolved, the severe complications of primary HIV infection in the CNS and opportunistic infection-related CNS sequelae have decreased. A few patients born prior to ART who had radiographic evidence of primary CNS HIV infection, such as enlarged ventricles, calcification of the basal ganglia and cortical atrophy as young children, and later in childhood were treated with HAART have achieved postgraduate educational levels. In spite of HAART HIV infected children remain at risk for poor school performance, developmental delay and behavior problems. Monitoring of and early identification of neurocognitive abnormalities as well as medical and psychosocial interventions are key to ensuring optimal quality of life in preventing such impairments.

Conclusion

Perinatally infected HIV-1 positive children are growing up in a new era with better treatment options, longer survival rates and improved quality of life; however concerns and challenges still exist. As we have shown above, this aging population has many new problems and issues which we are learning about, along with these children as they grow older. Regardless, more pediatric studies are needed to determine the effect of these treatment options and the disease itself in children who are living with it, surviving longer and going on to have their own children. The picture of HIV infected children is no longer as bleak as it was in the 1980s, but we still have many milestones to go before we can fully comprehend the effect of this disease and its treatment on HIV infected children, in both resource-plentiful and resource-challenged regions.

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4.2

Neurodevelopmental, Neurocognitive and Neuropsychological Outcomes in Adolescents with Perinatal HIV-1 Infection

Gail Burack, Roseann Marone

Introduction

Approximately 2.5 million children worldwide are living with HIV/AIDS, with another 2000 children becoming infected each day. In 2007 alone, just under one half million adolescents and young adults contracted HIV. While the majority of children with HIV live in sub-Saharan Africa, large numbers also reside in the Caribbean, Latin America and South/Southeast Asia. Most children living with HIV (around 90%) have acquired the virus through mother to child (vertical) transmission, either *in utero*, intrapartum or through breastfeeding.[1] HIV is also known to be neurovirulent, and has an adverse impact upon the developing central nervous system. This fact, along with the large number of HIV infected children and adolescents warrants an investigation of the neurodevelopmental outcomes associated with perinatal HIV infection.

Children are considered to be especially vulnerable to the adverse neurodevelopmental effects associated with HIV/AIDS, presumably due to the immaturity of the developing nervous and immune systems.[2] Despite this increased susceptibility, there is a paucity of studies focusing upon neurodevelopmental outcomes in HIV infected children and adolescents. The available literature has clearly demonstrated, however, that the HIV virus can adversely affect the developing CNS, and result in adverse developmental, cognitive and behavioral consequences.[2,3] The ability of the HIV virus to cross the blood brain barrier impacts CNS functioning and also increases the likelihood that infected children will have associated neurodevelopmental conditions. The implications of these morbidities are just beginning to be appreciated in the United States, particularly as the group of perinatally infected children enters adolescence and adulthood. This chapter will examine the neurodevelopmental sequelae associated with perinatally acquired HIV-1 infection in children and adolescents. Implications for long-term health and psychosocial outcomes will be discussed, particularly in terms of this cohort's ability to manage their disease and effective transition to adult life.

Since the introduction of combination antiretroviral therapy in 1996, more children and adolescents with vertically transmitted HIV-1 infection, living in the developed world, are surviving to adulthood. In the 1980's, during the early stages of the AIDS epidemic, adverse neurodevelopmental outcomes were commonly described for HIV infected children. Prior to the introduction of antiretroviral medications, progressive HIV-1 encephalopathy was reported in 35-50 percent of children diagnosed with AIDS.[4] With the utilization of Highly Active Antiretroviral Therapy (HAART), progressive encephalopathy can be prevented and, in some cases, reversed; however, neurodevelopmental manifestations of HIV infection can still persist. HAART is presumed to prevent CNS disease by suppressing systemic viral replication which in turn can prevent HIV carrying cells from invading the CNS and causing cortical atrophy.[1] The HIV virus, however, seems to have an affinity for the CNS which can serve as a reservoir for persistent HIV-1 infection. In addition, while some antiretroviral agents are able to cross the blood brain barrier (BBB) and inhibit viral replication, as well as the neurotoxic effects of the HIV virus, not all antiretroviral medications are able to do so. Protease inhibitors, in particular, are noted to have poor CNS penetration. Patients must also be >95 percent adherent with medication regimes in order to prevent the neurotoxic effects of the HIV virus.

The mechanisms of pediatric HIV-1 neuropathogenesis in perinatally infected children are not well understood. It has been demonstrated, however, that HIV progresses faster in children than adults and causes a higher incidence of adverse neurodevelopmental outcomes.[2] Children who are vertically infected also appear to develop clinical

symptoms faster than those infected by transfusion of blood products.[2,5] One of the reasons the HIV virus is presumed to rapidly impact the maturing nervous system of the young child is believed to be due to the incomplete myelination of the young central nervous system, which leaves it more vulnerable to insult.[6]

It is well documented that HIV-1 invades the CNS shortly after the time of initial infection via infected monocytes/macrophages and CD4+ T lymphocytes. Most HIV-1 detected in autopsy brain tissue has been found within the perivascular macrophages and microglia. Products such as viral proteins, proinflammatory cytokines and nitric oxide released from HIV infected macrophages and microglia, can lead to a sequence of neurotoxic events. In addition, HIV-1 can infect astrocytes in a CD4 independent and nonproductive manner. It has also speculated that the developing nervous system is more susceptible to alterations in astrocyte function, and that fetal astrocytes may be particularly susceptible to HIV-1 infection.

The most common Computer Tomography scan findings in perinatally infected children are basal ganglia calcifications, brain atrophy with enlarged ventricles and enlarged cortical sulci.[7,8] Magnetic Resonance Imaging findings have also shown HIV infected children to have a higher incidence of ischemic strokes and cerebral artery aneurysms.[8,9] In addition, the relatively long lifespan of macrophages, microglia and astrocytes, compared to CD4+ T cells, can pose a problem for fast elimination of the virus as HIV infected cells can continue to produce virus, viral RNA and potentially neurotoxic viral or cellular proteins over the life of the cell[4] (Figs 4.2.1 and 4.2.2).

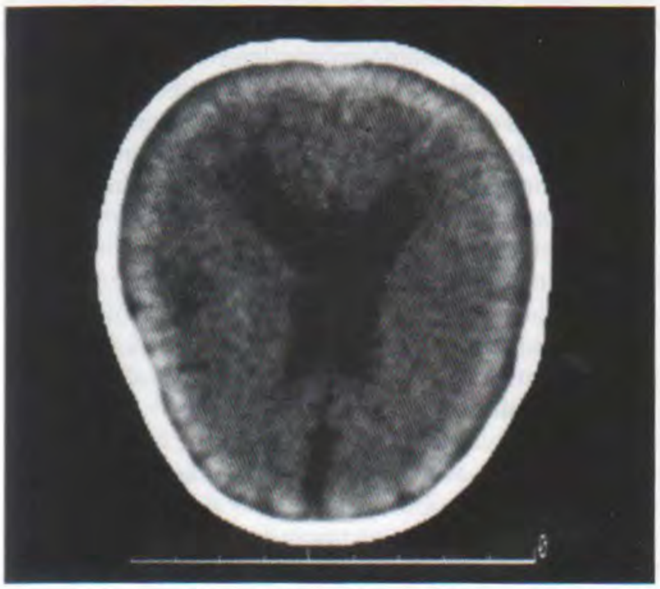


Fig. 4.2.1: Cerebral atrophy and dilated ventricles

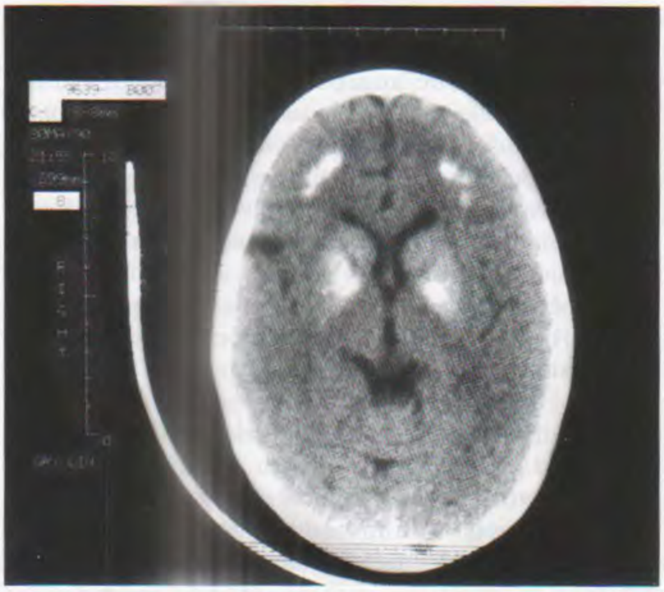


Fig. 4.2.2: Subcortical and basal ganglia calcifications

Since perinatal HIV infection was first identified in the 1980's, HIV-related encephalopathy has been recognized as a commonly occurring sequelae associated with the disease.[10] Two types of encephalopathy have been described in the literature-progressive encephalopathy and static encephalopathy. Progressive HIV encephalopathy (PHE) is the most severe and debilitating form associated with HIV-1 infection, with most children showing a significant decline in neurocognitive scores, loss of developmental milestones, acquired microcephaly, and/or abnormalities in gross motor skills by 18 months of age. Progressive encephalopathy often results in early mortality. The neuroradiological hallmarks of PHE include cortical atrophy and basal ganglia calcifications on computer tomography scans, as well as white matter lesions and central atrophy on magnetic resonance imaging.[4]

In contrast, children with static encephalopathy (SE), exhibit fixed, nonprogressive abnormalities in gross motor skills, learning abilities and/or developmental milestones.[10]

Progressive encephalopathy has been further divided into two different types (subacute and plateau) to describe distinct rates of disease progression seen in infants and children.[6] With advances in treatment, subacute progressive encepahalopathy is rarely seen in the United States, however is characterized by a progessive decline in all areas of neurodevelopmental functioning, a loss of already attained developmental milestones, and in some instances, death.[6] In the plateau type, children typically do not display regression in neurodevelopmental functioning but often fail to acquire new developmental milestones.

Prior to the availability of combination antiretroviral therapy, the prevalence of progressive encephalopathy was reported to be approximately 30-50 percent of perinatally infected children, with static encephalopathy estimated to be about 90 percent. With the advent of combination antiretroviral therapy, utilizing at least 3 antiretroviral agents, there have been significant improvements in survival and morbidity for these children. Since 1996, fewer children in the United States have been diagnosed with progressive encephalopathy. Studies have also shown an improvement in cognitive status since the use of combination antiretroviral therapy.[11]

In addition to the encephalopathic processes described above, children with HIV/AIDS are also vulnerable to other neurological diseases associated with their deficient immune status. With prophylactic treatment, the incidence of these disorders has declined, however co-infections such as cytomegalovirus, CNS lymphomas and toxoplasmosis can occur.[6] It should also be pointed out that even in countries with readily available medication and treatment, encephalitis, and its associated neurocognitive effects can still emerge when treatment adherence is suboptimal.

Although youth are believed to be more vulnerable to the neurotoxic effects of HIV-1 infection, the vast majority of studies have focused upon adults with HIV-associated dementia. HIV-associated dementia is a neurological disorder commonly associated with HIV infection and AIDS. It is reported to be a metabolic encephalopathy which is fuelled by the immune activation of brain macrophages and microglia.[12] HIV infected cells are believed to secrete neurotoxins which results in cognitive impairment, motor dysfunction, speech problems and behavioral changes. HIV dementia in adults can occur after years of HIV infection and is associated with low CD4+T cells and high plasma viral loads. As with HIV encephalopathy, HAART has been reported to prevent or delay the onset of HIV dementia in adults and can also improve cognitive functioning.[13]

It is not possible to predict which children may develop HIV related CNS disease;[4] in part, because the studies designed to predict neurodevelopmental outcome in infected children have been confounded by the fact that many children also have a history of premature birth and/or prenatal exposure to drugs or alcohol. Factors which have been found to be associated with more severe CNS disease in children include status of maternal and child immune system, elevated CSF and plasma viral load, timing of infection, route of transmission and availability of treatment.[4] The risk of encephalopathy is also higher among HIV infected children born to mothers with more advanced disease, as measured by CD4+ cell count and viral load at the time of delivery. In addition, children with advanced immune suppression early in life as well as those with high plasma viral load in infancy exhibit higher rates of encephalopathy. Maternal drug and /or alcohol use, poverty, low maternal education and poor quality of the home environment, can also contribute to adverse neurodevelopmental outcomes.

Neurodevelopmental Outcomes

Studies focusing upon the neurodevelopmental outcomes in children with HIV infection[6] have reported both developmental delays and intellectual deficits. While the earlier studies consisted of small sample sizes and/or descriptive cases, more recent studies, using appropriate controls, have been conducted. These studies have found that infants with HIV-1 infection, compared to seronegative infants, exhibit marked developmental delays independent of other potential risk factors, such as environmental variables.[6] Poor neurodevelopmental outcomes are also more likely when children do not receive adequate medical treatment or have poor treatment adherence. In a prospective study of 114 HIV-1 infected children, Chase[3] found that HIV-1 infection was significantly associated with increased risk of developmental, cognitive and motor delays, independent of prenatal drug exposure or other environmental factors. In addition, it is remarkable that these neurodevelopmental delays found in this study occurred in the absence of severe stages of disease progression.

Delays in both fine and gross motor functioning have frequently been documented in symptomatic seropositve infants and children. This is not surprising given the involvement of the basal ganglia and associated circuitry, as well as the vulnerability of motor skills to disease processes. Symptomatic infants have been reported to exhibit muscle tone abnormalities, delayed rate of gross motor skill acquisition and, in some cases, skill regression. Preschool and school age children have also demonstrated abnormalities in gait and balance. During the middle-late stages of severe symptomatic disease, the ability to ambulate can be lost due to the involvement of the lower extremities and processes affecting the basal ganglia.[6] With the advent of ART, the frequency of occurrence of these impairments have become less common, although opportunistic infections can occur and can also produce motor complications.

The results of studies investigating the impact of HIV-1 on cognition are conflicting. Some studies, involving older children, have found to have a significant lowering of overall intellectual functioning, with scores within the Borderline and Mild Mentally Retarded ranges reported. In contrast, other studies[14] found no differences between a group of HIV-positive vs noninfected children in overall

intelligence for as long as eight years after the infection.[6] While the variables which modulate this variability are poorly understood at present, one hypothesis is that neurodevelopmental outcome is related to the timing of perinatal infection, i.e., infants infected earlier tend to exhibit poorer immunologic, virologic and clinical outcomes.

Smith et al[15] investigated whether timing of infection was related to neurodevelopmental outcome. Using longitudinal regression analysis, the authors investigated neurodevelopmental outcomes in 114 HIV-1 positive infants with early positive cultures vs. those with late positive cultures. The results suggested that infants who were probably infected *in utero* (early infection) had significantly lower neurodevelopmental scores, when followed over the course of 30 months after birth, than those infected during the intrapartum period (late infection). Lower neurodevelopmental scores in infants may also be predictive of mortality. Llorente et al,[16] in a study of 157 perinatally infected HIV-1 positive infants who had longitudinal assessments over 36 months, found that a baseline assessment conducted at 4 months was able to predict mortality, with greater mortality rates found in infants with the lowest developmental scores.

More recently, research has begun to focus upon the effects of perinatal HIV-1 infection upon neuropsychological status, and in particular executive functioning. The field of neuropsychology deals with the relationship between the nervous system and cerebral or mental functions such as language, memory, and perception. Executive functioning refers to the "ability to sustain or flexibly redirect attention, the inhibition of inappropriate behavioral or emotional responses, the planning of strategies for future behavior, the initiation and execution of these strategies, and the ability to flexibly switch among problems solving strategies.[1]

Executive functions are typically high-level abilities that influence more basic abilities like attention, memory and motor skills, which can be difficult to assess directly. Difficulties in vigilance and attention are often described for individuals with any type of brain damage,[16] which demonstrates the fragile nature of these neurological functions. A number of studies have found that HIV-1 infected children exhibit problems with sustained attention. Early studies, using the Wechsler scales (WISC-R) Freedom from Distractibility factor, have found relative weaknesses for seropositive children on this variable.[17] Another study found that HIV-positive children obtained lower scores on tasks related to attentional abilities on the Kaufman scales of intelligence (K-ABC) compared to HIV-negative controls born to seronegative mothers. These findings, however, could be confounded by the higher baseline rates of attentional difficulties in this population. It should also be pointed out that demographic and environmental factors could account for some of the neurodevelopmental and neurobehavioral difficulties found in studies. Factors which may contribute to poorer developmental outcomes include changes in caretakers, poverty, and inadequate academic experiences. However, given the vulnerability of attentional processes to neurological insult, it is reasonable to speculate that these functions are negatively impacted.

In a small study, children with HIV were found to have deficits in executive functioning compared to sero-reverters.[1] Children and adolescents with HIV-1 and hemophilia have also been found to exhibit greater difficulty exhibiting sustained attention on a continuous performance task compared to children with hemophilia without HIV. Children treated with HAART with a higher percentage of CD4 cells have also been found to have higher working memory and processing scores.

Jeremy et al[18] examined the relationship between neuropsychological functioning and viral load in 489 HIV infected children (ages 4 months – 17 years of age) who were clinically and immunologically stable who were treated for at least 16 weeks with antiretroviral therapy. Neuropsychological functioning was significantly poorer at baseline for the HIV infected children when compared with established age norms. Children with higher viral loads had poorer cognitive, fine motor and neurologic signs at baseline. After 48 weeks of treatment with PI-containing combination therapy, there was a dramatic virologic impact, however the effect on neuropsychological functioning was minimal, with a significant improvement noted only in the vocabulary score.

In a cross-observational study, 22 children with perinatally acquired HIV infection were administered a global intelligence test from the Amsterdam Neuropsychological Tasks program (ANT).[19] Compared with age-appropriate age norms, the mean IQ of the HIV infected children was found to be within the Average range; however, HIV infected children performed poorer on neuropsychological tests measuring executive functioning. Processing speed was found to be the most sensitive cognitive measure in relation to HIV disease. These data, while exploratory in nature, suggest that more subtle neuropsychological impairments exist in HIV infected children.

Memory problems,[20,21] as well as difficulties with expressive language and auditory processing, have also been reported in the literature. Although both receptive and expressive language deficits have been reported, more significant effects have been found in expressive language functioning. Wolters et al[22] found expressive language skills to be more vulnerable to insult compared to receptive skills for both encephalopathic and non-encephalopathic children. It should be noted, however,

that these studies relied upon caretaker report which is not always an accurate source of information.

Neurobehavioral Outcomes

Many descriptive and clinical studies have reported that HIV-1 positive children are at increased risk of behavioral difficulties. These studies, however, have been confounded by inadequate control groups, small sample sizes and the inability to control for potentially confounding variables.[6] Mellins et al[23] examined the effects of prenatal drug exposure and environmental factors in 307 children born to HIV-positive mothers (96 HIV infected; 211 seroconverters). Multivariate analyses comparing the Conners' Parent Rating Scales of HIV infected children with perinatally exposed controls from similar demographic backgrounds, failed to find a significant relationship between prenatal drug exposure, or HIV status, and poor neurobehavioral outcomes. The authors, therefore, concluded that although children with HIV-1 infections have a high incidence of behavioral concerns, however, neither HIV infection or prenatal drug exposure are responsible for these difficulties; instead, demographic factors have been found to be significantly related to neurobehavioral symptoms. In the United States, perinatally infected children tend to live in areas with low socioeconomic status, and often are in families confronted with poverty, problems with housing and inadequate nutrition. School districts in these regions tend to have fewer resources than more affluent areas, resulting in educational disadvantages. HIV/AIDS is also associated with unique psychosocial stressors and complexities due to the stigma associated with the disease and mode of disease transmission. For example, in the United States, the majority of perinatally infected children have mothers who have acquired the virus through sexual behavior, IV drug use, or by having sex with men who are IV drug users. Despite advances in HIV care and treatment in the developed world, there is still tremendous stigma and discrimination associated with the diagnosis. Families with children infected perinatally can experience significant levels of guilt associated with having transmitted the disease to their offspring.[6] Mothers of perinatally infected children must also follow with their own medical care while caring for their children, which can compromise the family's resources and result in considerable economic and psychological stress. Many perinatally infected children have lost parents to death and are living with other caretakers and so experience problems related to attachment, loss and bereavement.

Noyce et al[24] characterized the behavioral and cognitive profiles of 274 clinically and immunologically stable antiretroviral experienced HIV infected children, ages 2-17 years. Children were assessed for behavioral developmental and cognitive functioning. The most common behavior problems, as assessed with the Conner's Parent Rating Scale, included psychosomatic, learning hyperactivity, impulsive-hyperactive, conduct and anxiety problems. Mean cognitive scores, on the Wechsler Intelligence Scale for Children-III, were lower than established normal population norms, with mean Verbal IQ = 85, mean Performance IQ = 90, and mean Full Scale IQ = 86. The authors concluded that clinically and immunologically stable previously treated youngsters experienced more frequent behavior problems and lower developmental and cognitive scores. The authors acknowledge that the etiology of these difficulties is likely to be multifactorial including such variables as prenatal drug exposure, maternal educational level, changes in caregivers, lead exposure and poverty.

Very little has been published on the prevalence of more severe psychiatric illness among HIV infected children.[1] Gaughn et al[25] documented higher rates of psychiatric admissions among perinatally infected youth in the PACTG 219C cohort as compared to the general pediatric population and HIV negative but exposed children. The authors cite that of the 1,808 participants in the cohort, 32 had been hospitalized at some point in their life for psychiatric symptoms, with common reasons being depression and behavior disorders.

Psychiatric symptoms related to HIV are believed to be in part to the direct infection of the CNS with HIV but can also due to comorbid conditions such as opportunistic infections, neoplasms and cerebrovascular disease.[8] Prenatal insults can also occur from substance abuse, inherited mental health disorders, inadequate nutrition, poor prenatal care and environmental conditions.[26]

Research on children vertically infected with HIV suggests that rates of depression, anxiety, behavioral and social problems range from 12 to 44 percent in this population.[8,23] In an early study by Havens,[21] attention deficit/hyperactivity disorder was the most common psychiatric diagnoses among perinatally infected youths, occurring in 21 percent. Rates were also high in the control group, also suggesting the importance of genetics, prenatal substance use and tobacco exposure.

Treatment of psychiatric symptoms in children and adolescents with HIV/AIDS remains largely empirical.[8] As in noninfected children, treatment of mood, anxiety and attention disorders is typically with antidepressant and stimulant medications. There is no data to suggest greater efficacy of one medication over another in HIV infected youth. Psychiatric management of children and adolescents with HIV/AIDS becomes especially important when mental health symptoms interfere with treatment adherence. Although nonadherence to medical regimes in children and adolescents with a chronic illness is fairly common, in HIV disease, intermittent or poor adherence

can lead to viral replication, mutation and subsequent development of drug-resistance.Reported adherence rates for HIV-positive youth are variable, ranging from 28 to 90 percent.[8,27,28]

Recent Developments

With advances in HIV care and treatment, a new line of therapy has emerged with a distinct mechanism of action-specifically, the protease inhibitors.[6] PI's prevent viral replication by inhibiting the protease enzyme and preventing the infection of new cells. Combination therapy, which includes protease inhibitors taken with transcriptase inhibitors (i.e., HAART) tends to be most effective in treating HIV-1 infection as well as preventing adverse neurodevelopmental effects. Although effective against HIV-1, these treatments may not be entirely free of significant side effects, particularly with regard to mitochondrial damage.[26]

Studies investigating the effects of HAART in children[29] have failed to find differences in neurodevelopmental functioning in infants born to HIV-1 positive mothers who received zidovudine for 4 years compared to a placebo control group. However, other studies have reported neurodevelopmental problems in infants of mother who received prenatal AZT.[30] Future studies are clearly needed to elucidate the long-term impact of protease inhibitors on neurodevelopmental functioning.

As mentioned previously, not all antiretroviral therapies are able to cross the BBB with the same degree of efficacy, which can affect the likelihood of adverse outcomes. In addition, some recent reports have found declines in neurodevelopmental and cognitive functioning despite stable immune and virological functions.[6,31] In addition, children may not exhibit readily apparent signs of HIV related neurodevelopmental involvement, but may show mild or very subtle impairments in higher order brain functioning or behavioral impairment. Studies have found that among children who have undergone detailed neurodevelopmental and neurobehavioral evaluations, subtle cognitive deficits are evident. It is, therefore, important that children be monitored over time; in fact, for children living in countries without sufficient resources, neurodevelopmental and neurobehavioral assessments may be the only diagnostic procedure available, and may be the first indicator of neurodevelopmental impairment. Llorente[16] has also shown that neurodevelopmental markers can serve as independent predictors of mortality in infants and poor outcomes.

Our knowledge about the impact of HIV on the developing brain is continuously evolving. Ongoing research is needed to study the impact of new treatment modalities and their potential impact upon children. It is also important to ascertain whether neurodevelopmental outcomes are the result of HIV-1 infection, side effects of treatment and/or environmental and psychosocial factors. As the cohort of perinatally infected youth in the US reaches adolescence and adulthood, additional research is needed to examine the impact of the virus on neuropsychological functioning and higher order cognitive processes. These issues become particularly important as these individuals must cope with the complexities of modern day life, function in vocational settings and become independent in their ability to manage the complexities of their HIV disease. While clearly, the primary goal of HIV care and treatment is optimum immune functioning and the prevention of viral replication, it is also important to think about quality of life issues for this group of children.

It is noteworthy that most of the research on neurodevelopmental outcomes of children living with HIV disease has been conducted in the developed world, with very few studies being conducted in developing countries, where the majority of HIV+ children reside.[1] Children growing up in developing countries face many additional challenges which can further impact their neurodevelopment, such as the quality of prenatal care, increased prevalence of coinfections (malaria, tuberculosis and bacterial meningitis), access to medical care and treatment, adequate nutrition, and variability in the quality of education. Most studies in developing countries have also focused on the first two years of life, and primarily upon cognitive and motor development.[1] It should be noted, however, that similar restrictions plague research conducted in both developed and developing countries. Limitations include the lack of appropriate norms, small sample sizes, lack of appropriate control groups, use of screening measures rather than ongoing assessments. Within the developed world, children are experiencing lower rates of encephalopathy, however more subtle neurodevelopmental deficits are being described. This phenomenon necessitates a more comprehensive battery of tests assessing many different domain and functions. The ability to conduct comprehensive neurodevelopmental assessments in settings where resources are limited can also be impossible to do. Future research should therefore focus upon developing reliable and valid screening tools which can be used in both developed and developing countries.

Advances in HIV medication and treatment have made a significant impact upon reducing the prevalence and severity of CNS disease in children and adolescents with HIV.[1] However, research is still needed as these children and adolescents enter adulthood. Previous research has studied some of the cognitive and language functioning difference between youth with and without HIV, however, fewer studies have investigated the impact of HIV upon higher order cognitive functions such as

executive functioning and memory. The number of youth with behaviorally acquired HIV infection is also increasing in number and represent an important group to study. Research is also needed on the long term effects of ART on the CNS, particularly as the number of youth with perinatally acquired HIV are living longer and will continue taking these medications into adulthood.

Case Studies

CASE 1

Maya is a 17-year-old girl with a diagnosis of perinatally acquired HIV infection. Associated diagnoses which have been described include: HIV encephalopathy, borderline intelligence, behavior problems and depression. Current antiretroviral regimen consists of atazanavir, emtricitabine and tenofovir, fosamprenavir and ritonavir. Viral load was <48 copies/ml and CD4 was 940 cells/Cu.mm (35.7%).

The biological mother was an IV drug user who died when Maya was an infant. Maya was subsequently cared for by series of family members until the age of 12, at which point she was placed in foster care. Maya began to exhibit behavioral difficulties and ran away from various foster homes, at one point saying she had been physically and sexually abused in one of the homes. She has had inpatient psychiatric admissions for self-injurious behaviors, suicide attempts and auditory hallucinations. She was reportedly diagnosed with schizophrenia at age 15. Maya is now in a specialized therapeutic foster home. She in the 11th grade and receives special education services in school. She receives in-home counseling and is followed by a psychiatrist for medication management. She is currently taking quetiapine and citalopram for psychiatric symptoms.

Recent neuropsychological testing conducted with Maya showed her to be cooperative and oriented to time and place. During testing, Maya responded to questions appropriately and was able to follow directions. Attention and focus were found to be adequate upon evaluation.

Neuropsychological testing revealed borderline cognitive abilities with a Full Scale IQ of 76. Cognitive impairment was found to be impaired across several areas of functioning. Academic skills were found to be limited, ranging from the 1st to 25th percentiles. Reading skills were well below age and grade expectancies. Behavior ratings indicated problems with mood as well as problems with emotional regulation and control. Cognitive flexibility was found to be an area of difficulty, as were planning and sequencing skills. Significant difficulties were noted on tasks requiring verbal and visual memory.

Questions

1. Can all of the patient's difficulties be explained by HIV-encephalopathy?
2. Of the problems the patient is experiencing, which ones are more likely related to perinatally-acquired HIV infection?
3. Which other variables are likely to have impacted the patient's neurodevelopmental and neurobehavioral outcomes?
4. What are some likely prognostic outcomes for this patient?
5. Is this patient likely to be able to live independently as an adult? What types of support services will be beneficial for the patient?
6. Are there other tests or studies which may be helpful in this case?

Answers

1. Not, all of the patient's difficulties can be explained by HIV encephalopathy. HIV encephalopathy can be a contributory factor, and could account for some of the low cognitive test scores as well as problems with emotional regulation and control. It is, however, difficult to make precise statements about causality because, as with most patients, there are multiple variables. Conditions such as schizophrenia are believed to be genetically and biologically based; there is no evidence to suggest that HIV encephalopathy causes diseases such as schizophrenia.
2. As discussed in the chapter, the problems most closely associated with HIV encephalopathy are low cognitive scores, problems with executive functioning, and difficulties with behavioral and emotional regulation.
3. Other contributory factors include the possible biological history of mental health disorders, possible physical and sexual abuse, side effects of HIV, lack of a consistent caretaker, and psychiatric medications.
4. This patient will require long-term assistance with activities of daily living.
5. The patient will probably have difficulties functioning independently. She will need assistance with daily living, job training and assistance and counseling. She would benefit from case management and supervision from an agency dealing with individuals with multiple types of disabilities. She will also need assistance with disease management and treatment adherence.
6. MRI of the brain might be useful to determine neurological involvement.

CASE 2

Marcus is a 15 year old boy who was seen in the emergency room for gastrointestinal pain, diarrhea, weight loss, skin lesions on the trunk and extremities and fever. According to the family, Marcus's gastrointestinal symptoms have been occurring on and off for approximately one year. Prior to that time, Marcus was reported to have experienced frequent respiratory and ear infections. Both parents denied a family history of HIV, however upon testing, Marcus was found to be HIV positive. Marcus admitted to having one heterosexual encounter approximately one year ago. Patient was admitted to the hospital; viral load at the time of admission was 16,000

copies/ml (log 4.2). CD4 count was 5 cells/Cu mm. A CAT scan of the head was conducted while Marcus was in the hospital. The scan revealed generalized cortical atrophy with left parietal, subcortical white matter lucency, which was said to most likely represent HIV encephalopathy. The patient was reported to be receiving specialized education services in an urban school environment. He is reported to have missed school days due to frequent illnesses. Parents were tested for HIV; Marcus's mother was found to be positive.

A neuropsychological evaluation indicated low average cognitive scores with a Full Scale IQ=82. Academic testing revealed skills to be at approximately the 4th grade level (actual grade placement is 10th grade). Ability to sustain attention was found to be adequate. Tests measuring executive functioning were within the average range. Motor and visual-motor skills were found to be average. No significant behavior or emotional difficulties were reported or found upon testing, although some adjustment issues were noted related to Marcus learning about his diagnosis.

Questions

1. Which findings in this patient were consistent with the diagnosis of HIV encephalopathy?
2. Considering the lab values, and symptoms at the time of hospital admission, how long is the patient likely to have been infected?
3. What other information would be helpful to obtain about this patient?
4. What neurodevelopmental outcomes are likely given the finding of low average cognitive scores, adequate executive functioning and low academic achievement?
5. Can all of the findings on the neuropsychological evaluation be attributable to HIV-encephalopathy? What other variables may be contributory in this situation?
6. Following stabilzation of this patient's current medical status, what services need to be put in place to promote an optimum neurodevelopmental outcome?

Answers

1. Generalized cortical atrophy, and white matter lucency have been described for patients with HIV encephalopathy.
2. The lab values are suggestive of long standing HIV infection.
3. A comprehensive history needs to be obtained to determine route of disease transmission. A 15 years old boy with long standing infection is most likely to be perinatally infected; therefore, additional information from parents is needed.
4. The patient might have some difficulties in school and vocational functioning given the low cognitive and academic scores. The finding of adequate executive functioning and the absence of behavioral and emotional problems, however, is promising and suggests that some higher order cognitive functions are intact.
5. Although, this patient has documented HIV-encephalopathy, some of the neuropsychological findings could presumably be influenced by the fact that the patient has been sick and missed a lot of school. Environmental factors such as urban school environment and inadequate family resources could also be contributory.
6. The patient will need ongoing HIV care and treatment. He will continue to require special education services in school. He may need vocation training upon completion of school. He would benefit from HIV counseling and education as well as mental health services to help him cope with his diagnosis.

Case 3

Cindy is a 5-year-old female with a diagnosis of perinatally acquired HIV. She was born via an uneventful vaginal delivery to a 24-year-old mother who had tested negative in her first trimester, but who was exposed to HIV later in the pregnancy. The mother received adequate prenatal care.

Medical History

At ages 3 months, 5 months and 6 months Cindy was hospitalized for bronchiolitis, reactive airway disease and pneumonia. At 9 months, she was rushed to the local emergency room for respiratory distress and required 100 percent oxygen without relief of symptoms. A chest X-ray showed diffuse interstitial infiltrates. Cindy was transferred to the children's hospital and required mechanical ventilation. The chest X-ray was confirmed for *Pneumocystis carinii pneumonia* (PCP) and silver stain of the sputum was positive for PCP. At time of this admission her weight was less than the 3rd percentile. Immunological work-up revealed a positive HIV test and a viral load of 750,000. Repeat HIV testing revealed that Cindy's mother was HIV positive.

Cindy's treatment for the PCP was the standard 21 day course of trimethoprim/sulfamethoxazole and methylpredinsolone sodium succinate. She was on mechanical ventilation for 20 days and significantly improved with normal chest X-rays and no respiratory distress on room air. She developed pseudomonas and had a positive blood culture for a staphylococcus infection. Cindy was started on combination antiretrovirals which included lamivudine, nelfinavir, and zidovudine. A computerized scan of Cindy's brain showed mild atrophy.

Cindy developed an oral aversion due to prolonged intubation and required nasogastric feedings with a high calorie formula. Her initial evaluation in the intensive care unit revealed that she had gross developmental delay. She was not able to sit independently and unable to

adduct her legs in prone. She displayed developmental regression in all areas. She was no longer able to pull to stand, and was not able to crawl or babble.

Cindy was transferred to a pediatric rehab hospital for 30 days where she received physical, speech and occupational therapies as well as a feeding evaluation. She was discharged home with nasogastric feedings every 12 hours as well as weekly physical therapy.

A neurology consult at age 27 months reported that Cindy could now walk and run independently, however she walked on her toes. She was able to reach for objects with both hands and could speak up to 40 words. She was socially interactive and had good eye contact. Head circumference at 3 months was 39 cm, and at 12 months was 42.5 cm. Examination of Cindy's extremities revealed that her tone in her upper extremities was normal. In her lower extremities, she had increased tone in the tendoachilles. She had severe spasticity involving her ankles. Ankles could not be passively dorsiflexed. She had upgoing plantars. Her deep tendon reflexes were 2+ in her biceps, 2+ in her triceps, and 2+ in her ankles. There was no evidence of any ankle clonus. The neurological exam revealed that when Cindy stooped down to pick up objects, she did not bend her knees all the way exhibiting increased tone in her lower extremities. She showed mild hip adductor tightening. She also walked with exaggerated toe walking and exhibited some mild scissoring. MRI was recommended as was a referral to a physiatrist. Recommendation for Botulinum toxin injections was also made at the time of neurological exam.

Follow-up of Patient

The MRI revealed a single nonspecific bright focus on flair images in the right frontal region of unknown etiology or significance. Cindy's HIV disease has been fairly well controlled with viral load measurements between 48 to 4,000 copies/ml. CD4 counts have not been below 758 cells /mm^3. Serial casting was performed on two occasions, however the mother did not return for the third series. Cindy wears orthotics with an ankle hinge. She attends regular full day kindergarten and receives physical therapy two times a week in school. HIV medications include zidovudine, didanosine, and nevirapine. Medical care team has concerns related to medication adherence due to a recent increase in viral load to 2100 copies/ml.

Questions

1. What clinical indications in the child's first six months may be related to perinatally acquired HIV?
2. Were there any other concerning signs in the child's first nine months?
3. What other services will Cindy need for her education and physical rehabilitation?
4. What other tests can be performed to identify additional signs of static encephalopathy?
5. What are some possible outcomes for a child with HIV encephalopathy?

Answers

1. The early history of respiratory infections and poor growth suggest the need for further medical work-up to include HIV testing.
2. The later history of PCP pneumonia, pseudomonas, and staphylococcus infection are further suggestive of HIV infection.
3. Early on, the patient required rehabilitative services which included speech, physical and occupational therapies. When she turned 3 years of age, the patient was eligible for educational services and therapies through her local preschool due to her physical impairments. The patient continued to require physical therapy when she entered Kindergarten. She will continue to require rehabilitative services in those areas where her impairments impact daily living skills and educational functioning.
4. The patient would benefit from ongoing monitoring of her developmental status as well as a comprehensive neuropsychological evaluation to determine strengths and weaknesses, and need for services.
5. This patient will probably have some extent of physical impairment throughout her life. She is at risk of neuropsychological impairment with associated difficulties in cognition and academic achievement. She is also at risk of attentional and behavioral difficulties.

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SECTION

V

Management Issues of HIV Infected Children

5.1

An A, B, C, D Approach to Nutrition in the HIV Infected Child

Luise V Marino, Madhavi Sathe

Introduction

The aim of this chapter is not to provide a literature review on aspects relating to nutrition research within the field of Human Immunodeficiency Virus (HIV)/Acquired Immune Deficiency Syndrome (AIDS), but rather to provide a brief insight into aspects relating to clinical practice, which form the basis for an integrated approach to nutrition management of HIV infected children.

Professor Nigel Rollins, World Health Organization (WHO) and others have compiled a set of invaluable nutrition handbooks,[1-3] excerpts of which have been included in this chapter in Appendix 5.1.1. The guidelines provide a holistic nutrition management tool which are thoughtfully presented, and can be used in daily clinical practice. It is recommended that these guidelines be locally adapted and implemented to improve the nutrition care of these vulnerable children.

Malnutrition and HIV Infection

HIV infected children are at particular risk of severe malnutrition as they are still growing. In a South African cohort of severely immunosuppressed HIV infected children, 58 percent had a height for age Z (HAZ) score of <-2 (severely stunted),[4] similarly in a cohort from Botswana of HIV infected children 59 percent were severely wasted with weight for height Z (WHZ) score of <-2 and 75 percent were severely stunted with HAZ of <-2 Z scores[5]

Severe malnutrition impacts on immune function decreasing resistance to infection and the body's ability to manufacture immune cells, in addition to their co products (such as interleukins, interferons and complement) altering the host defence mechanisms. These are further altered through micronutrient deficiencies altering the efficacy of many metabolic pathways.[6] Up to 62 percent of HIV infected children have been found to have one or more micronutrient deficiencies commonly: vitamins A, B6, E and B12, zinc and copper.[4] Micronutrient deficiencies may accelerate the progression of HIV infection, worsening nutrition status.[6]

Declining nutritional status can be categorized into two categories of diminished food intake and altered metabolism. Adult studies have shown that calorie requirements increase as CD4 cell count decreases and those with a CD4 cell count of <200 cells/mm^3 had the highest requirements but are also the most likely to have an inadequate intake.[7] An Indian study reported that 59 percent of children experienced a loss of appetite with 56 percent of them experiencing weight loss.[8]

Esophageal candidiasis, dysphagia (difficulty in swallowing) and odynophagia (painful swallowing) are common in HIV infected children impacting on their ability to consume sufficient macro and micronutrients. Dysgeusia (altered taste) and anorexia (loss of appetite) is also common and has been linked to zinc and iron deficiency. In studies looking at the efficacy of single and multiple micronutrient supplementation for up to 6 months, appetite is significantly improved through the provision of either zinc[9] alone or by giving a multi-micronutrient supplementation.[6]

Other factors impacting on growth failure in HIV infected children are commonly malabsorption and gastrointestinal dysfunction, (which in children more commonly manifests are carbohydrate malabsorption (e.g. lactose) rather than fat, as seen in adults); reduced food intake as a result of an inability to eat due to oral and upper gastrointestinal opportunistic infections and or food insecurity; high HIV viral load and low CD4 count resulting in anorexia; increased energy expenditure, which in adults has been shown to be an additional 22 kcal/day per 1-log $_{10}$ copy/ml increase in HIV ribonucleic

acid (RNA) and 80 kcal day for those adults receiving highly active anti retroviral treatment (HAART) to those who were not, suggesting that both HIV and HAART independently increase energy requirements; and finally an increased expression of proinflammatory cytokines such as interleukins 1β, 6 and tumor necrosis factor alpha, which also cause anorexia and increased energy needs.[7]

Malnutrition and the progression of HIV/AIDS are closely linked, leading to growth failure, stunting and an early death if there is no appropriate nutrition/ medical intervention. When loss of lean body mass approaches 55 percent of normal, regardless of wasting, death is imminent and nutrition/ medical salvage therapy is often futile. It is therefore, imperative that nutrition support and appropriate ARV therapy is commenced on time in order to support ongoing growth and improving the child's quality of life.[5]

Micro and macronutrients deficiencies are common in HIV infected children, impacting on the progression of the disease leading to growth failure and increased risk of morbidity and mortality. Healthcare professionals should have a low threshold for implementing both nutritions and medical support as early as possible. A full medical and nutrition assessment should be completed the first time a child is seen, which should include a screen for growth failure, macro- and micronutrient deficiencies, access to food and the ability to eat. Interventions should be provided within the context of a nutrition care plan which should include regular follow-up.[5]

The most important aspects of nutrition support focus on early identification of growth faltering through the use of a nutrition screening tool, and the subsequent implementation of appropriate nutrition support strategies. A nutrition care plan, as the name suggest is a plan which requires entry to a course of action, review and eventually exit when the goals are achieved. The mainstay of dietary treatment includes: anthropometric ("A"), biochemical assessment ("B"), clinical ("C") and dietary ("D"), which will be discussed briefly in the following pages.

Nutrition in the HIV Infected Child

One of the most important factors relating to the survival of an HIV infected child is the health of the mother, which is not just specific to HIV infected children. An infant is dependent on their mother for care, nurturing, protection and nourishment which also include decisions around accessing healthcare facilities, feeding practices and other health protective interventions. In children, with severe malnutrition caregivers often come from socially dysfunctional backgrounds and as a result are less sensitive to the needs of their child.[10]

In communities, where there is a high prevalence of HIV infection, severe malnutrition is more common especially following the death of primary caregiver from HIV / AIDS. In mothers, where there is advanced disease children are more likely to die, irrespective of the child's HIV status. This is most acutely seen in the 12 months preceding her death, which suggests that as her own health declines she is less able to care for her children. Young orphaned children are also at high risk as they are often passed between family members in an effort to provide sustained care.[10]

Another aspect of child survival within this context is allowing women to have sufficient autonomy with respect to sexual and reproductive decisions as appropriate child spacing increases maternal social skills and opportunities which positively impact on child survival.[10]

Maternal Nutrition Status during Pregnancy

HIV infected women within a developing country often come from backgrounds of high food and economic insecurity. Poverty is common within these settings and with the increased burden of pregnancy, lactation and increased nutrition needs as a result of HIV infection, malnutrition may be common. Weight loss is associated with an increased risk of morbidity and mortality[11] and an increased risk of early mother to child transmission.[12]

Micronutrient supplementation is important in pregnant women, especially those from resource poor settings as nutritional deficiencies are associated with immune dysfunction and increased susceptibility to infection, faster HIV progression and possibly increased risk of vertical transmission of the virus to the unborn infant.[13] Two studies from Nepal and Tanzania showed when micronutrient supplementation was provided to HIV uninfected women there was a reduction in small for gestational age and reduced low birth weight infants. Another study reported that when high dose micronutrient supplements were given to HIV infected women with low lymphocyte counts and poor nutritional status there was a significant reduction in low birth weight infants and reduced HIV transmission through breastfeeding.[14]

Maternal HIV Infection and Anti Retroviral (ARV) Medication

An unequivocal way in which HIV infected women can be protected from dying is to provide early anti retrovirals (ARVs), especially to those with advanced disease (CD4 cell counts <200 cells/ml). In infants born to mothers with advanced disease their infants are 8 times more likely to become infected peripartum and postnatally, compared

to those with CD4 counts that were higher. Health outcomes can be improved by implementing the WHO two tiered approach for maternal treatment and prophylaxis.[10]

Infant Feeding and the Prevention of Mother-to-Child Transmission (PMTCT)

The area of infant feeding is very controversial. Breastfeeding is one of the most critical and crucial factors to infant survival. In recognition of the increased risk of morbidity and mortality from replacement feeds such as diarrheal disease and malnutrition, the WHO revised the AFASS statement (acceptable, feasible, affordable, sustainable and safe) in 2007 especially in the light of a significant body of new evidence relating to exclusive breastfeeding.

The main recommendations can be summarized as follows:

1. Exclusive breastfeeding for up to six months, there is an absolute risk of transmission of only 2 to 4 percent, which was significantly increased if there is mixed feeding and/or early introduction of complementary food.
2. Exclusive breastfeeding is recommended for HIV infected women for the first 6 months of life unless replacement feeding is acceptable, feasible, affordable, sustainable and safe for them and their infants before that time.
3. When replacement feeding is acceptable, feasible, affordable, sustainable and safe, avoidance of all breastfeeding by HIV infected women is recommended.
4. At six months, if replacement feeding is still not acceptable, feasible, affordable, sustainable and safe, continuation of breastfeeding with additional complementary foods is recommended, while the mother and baby continue to be regularly assessed. All breastfeeding should stop once a nutritionally adequate and safe diet without breast milk can be provided.
5. Whatever the feeding decision, health services should follow up all HIV-exposed infants, and continue to offer infant feeding counseling and support, particularly at key points when feeding decisions may be reconsidered, such as the time of early infant diagnosis and at six months of age.
6. Breastfeeding mothers of infants and young children who are known to be HIV infected should be strongly encouraged to continue breastfeeding.
7. Governments and other stakeholders should revitalize breastfeeding protection, promotion and support in the general population. They should also actively support HIV infected mothers who choose to exclusively breastfeed, and take measures to make replacement feeding safer for HIV infected women who choose that option.[15]

The WHO AFASS guidelines, e.g. acceptable, feasible, affordable, sustainable and safe have often been difficult to interpret especially at an operational level and in countries where there is a significant morbidity and mortality from replacement feeding.[16] Where women met the AFASS criteria, more specifically those who have piped clean water, fuel and disclosure of their HIV-1 status, there is the lowest risk of HIV-1 transmission. However, in women who did not meet the criteria, there is a significant increase in morbidity and mortality in infants who were both breastfed and replacement fed. In countries, where there is a high acceptance and uptake for breastfeeding, complete replacement feeding can often result in inadvertent disclosure of maternal HIV status in settings where breastfeeding is the standard practice and replacement feeding is not well accepted as has been seen in Pune, India.[14,16]

The new (WHO) AFASS statement places an increased recognition on the ability of the health care service within resource poor settings to provide all of the necessary care, counseling and support to women. When considering the type of feeds that will most suit an individual it is essential to take into account the social and economic circumstances in addition to her health. It is also necessary to understand the extent of support which will be provided by local health services in addition to the amount of individual health worker support she is likely to receive.[14]

Where PMTCT programs are in place which provide free replacement feeding for the first 6 months of the child's life, consideration on the financial implication imposed for the second 6 months of an infant's life need to be taken into account, as many infants become severely malnourished during this period as a result of inappropriate complementary feeding practices in addition to overdiluted replacement feeds and poor nutrient density of complementary foods.[14,16]

Often within resource poor settings, access to a safe water supply is less than reliable, increasing the morbidity and mortality from contaminated feeds. The safety of replacement feeding varies greatly and is dependent on the setting and resources available. In the Côte d'Ivoire comparable morbidity survival has been shown between replacement feeding and shortened exclusive breastfeeding. In Botswana, in 2006, replacement feeding was associated with a 50-fold increase in mortality as a result of abrupt changes in the safety of the water supply and availability of replacement feed.[14]

In addition to this, care practices around how to safely prepare infant formula within the home and hospital setting often result in highly contaminated infant formula. With expanded PMTCT programs, there is greater access

to ARVs, decreasing maternal viral load sufficiently to help mothers, decide that breastfeeding should be the feeding mode of choice especially within areas that are at risk of infrastructure failure.[14]

Shortened breastfeeding (6 months of age) and subsequent replacement feeding is associated with significant increased risk of mortality. As a result, indefinite breastfeeding should be considered as resulting from the ZEBS cohort, where infants were randomly assigned to either early cessation at 6 months versus indefinite breastfeeding showed that there was no increased risk of transmissions of HIV-1 in the indefinite breastfeeding group. Indefinite breastfeeding is associated with a transmission risk of 8.8 percent, which is offset by the mortality costs related with shortened breastfeeding.[14]

Antiretroviral Therapy during Breastfeeding

The WHO/UNAIDS guidelines for HIV-1 infected women recommend that women who meet the criteria for HAART should have the therapy initiated during pregnancy for the sake of their health, which should be continued indefinitely. For those women, who do not meet the HAART criteria, it is recommended that they receive a short course of zidovudine/ nevirapine with a short combined ARV "tail" to decrease the incidence of nevirapine resistance, which results in a low rate of vertical transmission ranging from 1 to 6 percent. Trials are ongoing to determine the efficacy of HAART during breastfeeding compared to zidovudine/nevirapine for mothers who are not immunosuppressed.[14]

Nutrition Status of HIV Infected Children

In children, HIV infection is associated with slower linear and ponderal growth in children younger than 2 years of age. Factors which were also found to predict linear growth retardation included level of maternal education, anaemia and diarrheal disease.[17] Careful attention to the nutrition requirements and subsequent intake is important if children are to achieve a good nutrition status and continue to thrive.

The A, B, C, D of a Nutrition Care Plan for HIV Infected Children

Overview

The following sections provide an overview of a practical approach to developing a nutrition care plan for HIV infected children.[18] The following sections should be read in conjunction with the WHO Chart Booklet for the integrated nutritional care for HIV infected children (6 months to 14 years).[1-3] Table 5.1.1 provides an overview

Table 5.1.1: An overview of the A, B, C, D approach to the nutrition care for HIV infected children

Clinical assessment: Factors to review
Anthropometry
• For children <5 years of age review their road to health card and record growth trend • Measure weight, height/length, Head circumference <3years MUAC 1-5 years • Plot length/height, weight and HC on age and syndrome appropriate growth chart in patient's medical notes, use WHO percentile charts • Calculate percent Weight for height, percent weight for Age, percent Height/length for Age and Height Age • Classify patient's anthropometry using WHO Z scores and waterloo for height for age and weight for height and Gomez criteria for weight for age, record in medical folder • If there is moderate-severe wasting or stunting implement nutrition care plan A, B or C • Determine weight loss or gain or failure to thrive since previous visit and record in child's records • Determine appropriate nutrition care plan for the patient based on nutrition risk, e.g. weight maintenance or providing sufficient calories to promote catch up growth
Biochemistry
• Review available biochemistry making special notes of deranged results where appropriate, e.g.   - Glucose   - Lipogram   - Full blood count • When recording nutrition care plan, provide appropriate dietary recommendations, e.g. around iron deficiency or other related anemias, elevated glucose levels. • Determine whether other medication is being taken and potential drug-drug or drug nutrient interactions, e.g. over the counter medication and or traditional medicines
Clinical
• Record medical diagnosis in addition to comorbid disease states and/or complications, e.g. TB or type II diabetes • Complete a thorough clinical exam, making note of skin, hair, fat distribution changes
Dietary
• Determine patient's dietary requirements, factoring in an increase or decrease in requirements where required, using either Schofield equation or DRI's plus a 10, 20-30% or 50-100% factor • Annotate dietary requirements in medical notes • Record a diet history at each review noting any changes in eating habits, amounts of food consumed • Determine food security using WHO Screening tool • Recommend nutrition care plan A, B, or C according to chart booklet and provide appropriate supplementation where required • Record type of supplement provided, amounts to be consumed daily, calories provided in addition to meals

Contd...

Contd...

- Referral to a nutrition supplementation scheme, if growth faltering
- Recommend review time within notes and to caregiver, e.g. monthly visits

Follow-up

- Weekly—in a child with moderate to severe malnutrition or infant with failure to thrive
- Monthly—if an infant or child with moderate to severe malnutrition with previous failure to thrive is growing well
- If growing well—follow up according to the growth monitoring protocol (0-2 years—monthly, >2 years—quarterly)

of aspects involved in the nutrition care of HIV infected children and can be used as a checklist.

Anthropometry

Malnutrition negatively impacts on a child's cognitive and behavioral development, intellectual achievement and functional ability later in life resulting in decreased economic output and increased mortality and morbidity rates.[19] The following section describes the various anthropometrical measurements and their interpretations.

Nutrition Assessment in Young Children

Nutritional status may be measured using a number of different parameters such as clinical signs, biochemical indicators or anthropometry. The benefits of using anthropometric measurements over clinical and biochemical signs are that they are relatively noninvasive, cost less and easier to obtain compared to the other two.[19]

Stunting may be viewed as a long-term indicator of chronic undernourishment and a high prevalence within a population is associated with poor socioeconomic conditions and overall social deprivation. Wasting is reflective of an acute problem and is often sensitive to nutrition intervention programs. Children who are underweight may be more difficult to interpret, as it is not reflective between temporary and long-term malnutrition. If within the population the rate is low it may be interpreted as a chronic condition similar to height for age.[19]

Height, weight and age are necessary components to determine three key anthropometric measurements: weight-for-height, height-for-age and weight-for-age, these can then be expressed in Z-scores.[19] The calculation of WHZ is often difficult to achieve. Height measures are difficult to take often as a result of few trained healthcare professionals within a busy healthcare setting. In addition to this, the accurate measure of weight relies on a calibrated scale which may not be available. If these two measures have been achieved in order to calculate WHZ score, a 3rd value needs to be looked up on a chart and correlated with the findings. Conversely, taking a mid upper arm circumference (MUAC) reading is a relatively simple, cost effective objective measure to collect which enables the assessment of nutrition status and has high corresponding specificity and sensitivity to WHZ.[20]

Normal Growth in Infants and Children

It is important to determine whether or not a child is growing appropriately, especially during the first year of life. Normal birth weight averages between 3.3 kg and 3.5 kg in the western setting; infants with intrauterine growth retardation (IUGR) or small for gestational age are normally below 2.5 kg. In central Asia, low birth weight infants (LBW) make up 30 percent of all live births, however expected growth velocity post birth should be normal.[21]

Measurements at birth should include weight (wt), length (lt) and head circumference (HC) which should be recorded in the infant's road to health chart (RtHC). During the first 5 to 7 days, there is some weight loss but birth weight is normally regained by the tenth to the fourteenth day. Many growth charts are misleading as they do not allow for neonatal weight loss in the first two weeks of life. Test weighing before and after breastfeeding in addition to top up replacement feeding is of little value and may undermine breastfeeding practices. During the first 4 months a full term infant normally doubles its birth weight at 4 months and at 12 months is triple that of the birth weight. Table 5.1.2 provides a summary of ideal weight gain in grams of a healthy term infant during the first year of life.[22]

Length is an important marker of growth and stunting is indicative of chronic malnutrition. At 12 months of age, the length is normally 1.5 times than that at birth. At 5 years birth length is doubled. The following growth rates are expected up to puberty; 25 cm during the first year of life; 12 cm during the second year of life and 10 cm per year, steadily declining to 6 cm until the growth spurt at puberty.[22]

It is recommended that recumbent length is measured using an appropriate measuring mat if the child is <85 cm or <2 years old. Standing height (measured with stadiometer) can be undertaken in children >85 cm or above 24 months, although some may not be able to lock their knees to be able to stand up straight and recumbent length can be measured up to the age of 3 years.[22]

Table 5.1.2: Ideal weight gain in gram per week for healthy term infants[22]

Months	*Weight gain per week*
0-3 months	200 g per week
4-6 months	150 g per week
7-9 months	100 g per week
10-12 months	50-75 g per week

Growth Faltering (GF)

In order to determine growth faltering (GF), a growth trend is required as a single measurement might indicate absolute shortness and tallness whereas two or more measurements over a period of time are able to detect a change in growth.

The definition of GF from birth to 18 years may be as follows and should be documented accordingly:

- 0 to 6 months: the growth curve flattens or drops over two consecutive visits on the Road to Heatlh Card (RtHC)
- 6 to 12 months: the growth curve flattens or drops over two consecutive months on the RtHC
- 1 to 5 years: the growth curve flattens or drops over two consecutive months on the RtHC
- 6 to 14 years: the growth curve flattens or drops over two consecutive months on the wt for age growth chart.

Interpretation of Growth Charts

Interpretation of growth charts may display a horizontal, descending or sharp ascending line. These features should be documented in the nutrition care plan within the medical notes:

- **Horizontal line**—No growth; dangerous sign; first sign of moderate or severe malnutrition or disease; follow-up and nutrition education is needed.
- **Descending line**—Decrease in growth; very serious and needs immediate attention.
- **Sharp ascending line**—Improvement or on the way to overweight or obesity.[23]

The pictorial examples in (Fig. 5.1.1) show growth charts of a child who is growing well, growth faltering, e.g. crossing growth lines and growth failure, e.g. losing weight. Table 5.1.3 provides some general criteria for quantifying growth failure in terms of the length of time, there has been no weight gain for in addition to any documented weight loss.

Growth Velocity

- The growth curve of the child can provide information on the varying rate of growth with age.
- This rate of growth is generally termed the "growth velocity".
- This helps to detect abnormal changes in growth and to evaluate individuals in terms of changes in rates of growth and response to nutritional therapy.[23]

Factors Leading to Growth Faltering

Children presenting with growth faltering, e.g. crossing centiles, plateauing or fluctuating weight should have a thorough medical taken including aspects around dietary history, including food frequency and food recall, in addition to aspects around the family's food and household security. There are many reasons for growth faltering, amongst which, chronic illness and food insecurity are the greatest cause for concern.

Common causes for inadequate nutrition resulting in growth faltering are:

- Chronic Illness
- Poverty
- Poor routine
- Lack of knowledge
- Inadequate access to food
- Feeding problems
- Family problems
- Maternal influences.[19]

Table 5.1.3: Criteria for growth failure[23]

Age group	*No weight gain for*	*or loss of weight of*
Birth-3 months	2 weeks	100 g
4-6 months	1 month	250 g
7-12 months	6 weeks	500 g
13-24 months	3 months	1 kg

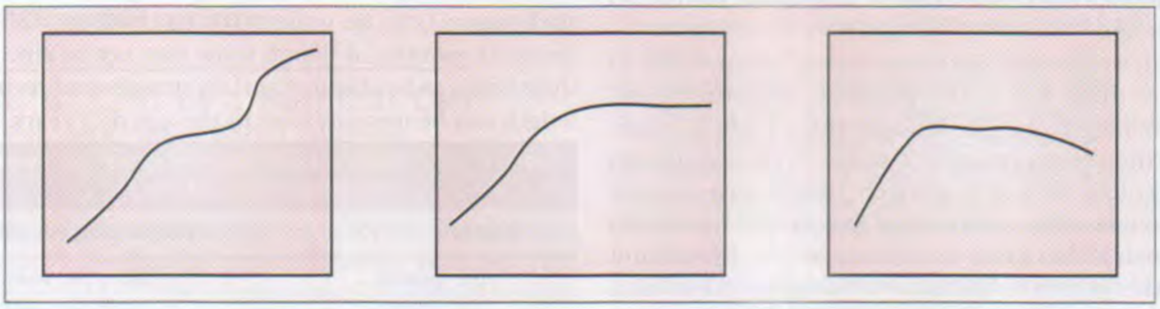


Fig. 5.1.1: Examples of growth curves: Growing well, growth faltering and growth failure[1]

Table 5.1.4: WHO Classifications of moderate and severe malnutrition[24]

	Classification	
	Moderate malnutrition	Severe malnutrition
Symmetrical edema	No	Yes Edematous malnutrition
Weight-for-height	-3 < Z score < -2 Z score 70-79% moderate wasting	< 3 Z score < 70% severe wasting
Height-for-age	-3 < Z score - < -2 Z score 85-89% moderate stunting	< 3 Z scores < 85% severe stunting

Classifications of Malnutrition

Malnutrition can be classified in a number of ways, however it is suggested that WHO criteria be used (Table 5.1.4) including the more recent terminology of severe malnutrition with severe wasting or edematous malnutrition. Malnutrition can be classified using either Z scores or percentage of expected weight for height or height for age.[24] If a child is found to be severely malnourished, a test feed should be given. If the child manages to consume the test feed the child can be successfully managed with the community using ready to use therapeutic paste based on the recipe provided in the manual: WHO Community Based Management Guidelines of Severe Malnutrition.[25] However, if the child lacks an appetite and fails a test feed the child should be admitted to an appropriate healthcare facility for in hospital management of severe malnutrition using the WHO 10 steps.[24]

There are various ways in which to interpret anthropometrical measurements and Table 5.1.5 provides a guide which may be used when interpreting individual measurements.

Mid Upper Arm Circumference (MUAC)

MUAC is often a measurement that is often more readily achievable especially in resource poor settings. Extremities such as arms are less affected by edema and as such MUAC is a useful measure in edematous malnutrition. Table 5.1.6 provides cut-offs for the use of MUAC in moderate and severe malnutrition.[20]

Biochemical

Biochemistry should be completed on all children according to local protocol. Table 5.1.7 provides a summary of CD4 results in relation to the degree of immunosuppression.[26]

Table 5.1.5: Interpretations of Weight-for-Age, Height-for-Age, Weight-for-Height and Height-Age[23]

Index	Use	Low	High
Wt-for-Age	This reflects body mass relative to chronological age. Weight-for-age is an indicator for underweight, however should be used in context with height/ length or as a trend to provide any meaningful insight into the child's nutrition status.	A low wt-for-age is termed underweight.	A high wt-for-age is seldom used as an index, since an increased wt-for-ht is more accurate in determining overweight and obesity.
Ht-for-Age	This reflects achieved linear growth. Height-for-age describes linear growth and may be reflective of stunting and chronic malnutrition	A low ht-for-age can be due to shortness (due to a normal variation or a pathological process) or stunting (a failure to reach linear growth potential due to undernutrition).	A high ht-for-age or tallness is of little clinical concern unless due to endocrine disorders.
Wt-for-Ht	This reflects body wt relative to current ht. Weight for height describes wasting, which is normally reflective of acute malnutrition.	A low wt-for-ht can be due to thinness (not due to a pathological process) or wasting (due to acute starvation or disease).	A high wt-for-ht is either overweight or obesity. Although, a high wt-for-ht can be due to an increased lean body mass, it can still be used as an indicator for obesity.
Ht-Age	This is the age at which the current ht falls on the 50th percentile on the lt-or ht-for-age growth charts. Ht-age is used in calculations of nutritional requirements in children who are much smaller than their chronological age, e.g. those with renal failure.		

Table 5.1.6: MUAC reference ranges for moderate – severe malnutrition[1-3,35]

MUAC reference ranges for moderate to severe malnutrition 6 months -14 years-old		
Infants 6-12 months	• Is MUAC less than 110 mm?	Severe malnutrition
	• Is MUAC less than 115 mm?	Moderate malnutrition
Children 1-5 years	• Is MUAC less than 110 mm?	Severe malnutrition
	• Is MUAC less than 135 mm?	Moderate malnutrition
Children 6-9 years	• Is MUAC less than 135 mm?	Severe malnutrition
	• Is MUAC less than 155 mm?	Moderate malnutrition
Children 10-14 years	• Is MUAC less than 160 mm?	Severe malnutrition
	• Is MUAC less than 185 mm?	Moderate malnutrition

Table 5.1.7: CD4 levels in relation to the severity of immunosuppression[26]

HIV associated immunodeficiency	*Age*			
	≤11 months (% CD4+)	*12-35 months (% CD4+)*	*36-59 months (% CD4+)*	*5 years or over (absolute number per mm ^{3} of CD4+)*
None or not significant	>35	>30	>25	>500
Mild	30-35	25-30	20-25	350-499
Advance	25-29	20-24	15-19	200-349
Severe	<25	<20	<15	<200

Table 5.1.8: Summary of blood cholesterol/ lipogram, hemoglobin, lactate and blood glucose

Blood test	*Normal range*
Blood cholesterol	3.8-5.7 mmol/l (Target <5 mmol/l)
Triglycerides	0.9-1.97 mmol/l
LDL	<3.37 mmol/l (target <3 mmol/l)
VLDL	Used to determine LDL
HDL	Target >1.5 mmol/l
HDL: LDL	>0.24 mmol/l
HDL: Total Cholesterol	1:3 of >0.20 mmol/l
Hemoglobin	11-13 g/l
Lactate	<2.5 mmol/l
Blood glucose	3-5 mmol/l

Biochemical Assessment for Lipodystrophy

As lipodystrophy is anticipated to affect 25 percent of children receiving ARVs, especially proteases inhibitors (PIs), it is important that biannual blood parameters are reviewed (Table 5.1.8). Lactic acidosis is a severe and potentially fatal complication, which may arise; however, children should be treated clinically and routine lactate levels currently serve no purpose.[19]

As significant weight gain and considerably more slowly linear growth is anticipated in children following immune reconstitution after ARVs have been commenced, it is important to monitor for early signs of overweight/ obesity and the development of a metabolic syndrome, including diabetes (Table 5.1.8). If the child was previously very malnourished some aspects of the nutrition care plan will need to be revised in order to revert to a healthy balanced diet based around food based dietary guidelines (Dietary Section).[19]

Clinical

Classification of HIV/AIDS in Pediatrics

Pediatric HIV differs from that of adults in several ways, the time from exposure/ infection to symptomatic disease is shorter, bacterial infections and lymphocytic pneumonia are more common. Recurrent infections are common such as chronic gastroenteritis.[26]

Clinical Assessment

Children often present acute-on-chronic malnutrition, with growth failure, e.g. stunting and wasting. In addition, developmental delays and swallowing difficulties are common. Multiple members of a family unit may be affected and or primary care givers may also be sick and or have died resulting in increased risk of food insecurity. It is important to complete a thorough clinical assessment to establish whether the child has concomitant micronutrient deficiencies. Table 5.1.9 may be used to classify clinical signs of macro and micronutrient deficiencies found in the malnourished child.[27] Where clinical signs of vitamin and mineral deficiencies are present micronutrient supplementation should be implemented as per local protocols, e.g. a single high dose vitamin A and a two week course of zinc (10 mg/day

Table 5.1.9: Clinical signs and symptoms in the malnourished child[27]

Clinical sign	*Suspect nutrient*	*Clinical sign*	*Suspect nutrient*
Epithelial		**Ocular**	
Xerosis, dry scaling	Essential fatty acids	Pale conjunctiva secondary to anemia	Iron, folic acid, vitamin B12, copper, vitamin A
Hyperkeratosis, plaques around hair follicles	Vitamin A	Bitot's spots (grayish white or white foamy spots on the whites of the eyes)	Vitamin A
Ecchymoses, petechiae	Vitamin K, C	**Musculoskeletal**	
Hair		Muscle wasting, prominence of body skeleton, poor muscle tone	Protein, calorie
Easily pluckable dispigmented, lackluster	Protein, calorie	**General**	
Nails		Edema	Protein
Thin, spoon-shaped	Iron	Pallor secondary to anemia	Vitamin E, iron, folic acid, vitamin B12, copper
Mucosal		**CNS**	
Mouth, lips and tongue	B Vitamins	Mental confusion	Protein, thiamine
Angular stomatitis (inflammation at the corners of the mouth)	Riboflavin	**Cardiovascular**	
Cheilisis (reddened lips with fissures at angles)	Riboflavin, vitamin B6	Beriberi (enlarged heart, congestive heart failure, tachycardia)	Thiamine
Glossitis (inflammation of the tongue)	Riboflavin, Niacin	Tachycardia secondary to anemia	Iron, folic acid, vitamin B12, copper, vitamin E
Magenta tongue	Riboflavin	**Gastrointestinal**	
Edema of the tongue, tongue fissures	Riboflavin	Hepatomegaly	Protein, energy
Gums		**Glandular**	
Spongy, bleeding	Vitamin C	Thyroid enlargement	Iodine

for <1 year of age and 20 mg/day for >1 year of age) for diarrheal disease.[28]

Dietary

Indian Food Pattern

India is a vast country. The main occupation is agriculture which is dependent on the monsoon. Type of food intake, eating habits and cooking methods are influenced by a number of factors such as locally available foods and seasonal availability of food, religion, customs and traditions, socio-economic status and so on. There is a difference in the food eaten in urban cities, semi urban areas, villages and the tribal areas. Though, different regions have their own unique cuisines, there are some similarities.

The Indian diet is cereal based with pulses, vegetables, nonvegetarian foods and milk and milk products making up the "accompaniments" in a meal (Table 5.1.10). The accompaniments include chutneys, salads, dals or pulse preparations, vegetable gravies, meat, fish or chicken gravies and sweets. Sweets are not eaten separately as dessert but form a part of the meal. Pickles made from a variety of fruits and vegetables and papads (a dehydrated food made from pulses or cereals, can be deep fried or roasted to give a crisp product like potato chips) form an integral part of the diet.

Different types of oils, butter, ghee (clarified butter) are used to cook the recipes. Most Indian cuisines have their own spice mixes that are made in bulk and stored. These are added to pulses or vegetables or other preparations. Special foods are made for different festivals and occasions. Food is also different on "fasting" days.

A variety of tropical and subtropical fruits like bananas, custard apple, jackfruit, guava, sapota, mangoes, apples, pears, apricots, grapes are also consumed. Though, their consumption is affected by seasonal availability and fruits are expensive so consumption is less in people especially from low socioeconomic levels. After a meal, mukhwas (after-mint) in the form of supari or paan is eaten.

In the northern states of India, the main cereals consumed are wheat, maize and rice. Meat and fresh water fish also form a part of the meal. Oil used for cooking is generally mustard oil. Vegetables are incorporated as gravies, chutneys and salads. Nuts like walnuts and

Table 5.1.10: Recommended dietary allowances for Indians: Given by Indian Council for Medical Research (ICMR), New Delhi

Group	Particulars	Body Weight (kg)	Energy (kcals)	Proteins (g)
Man	Sedentary Work		2425	60
	Moderate work	60	2875	
	Heavy Work		3800	
Woman	Sedentary Work		1875	50
	Moderate work	50	2225	
	Heavy Work		2925	
	Pregnancy		+ 300	+ 15
	Lactation: 0-6 months		+ 550	+ 22
	6-12 months		+ 400	+ 18
Infants	0-6 months	5.4	108 kcal/kg	2.05 g/kg
	6-12 months	8.6	98 kcal/kg	1.65 g/kg
Children	1-3 years	12.2	1240	22
	4-6 years	19	1690	30
	7-9 years	27	1950	41
Boys	10-12 years	35.4	2190	54
Girls	10-12 years	31.5	1970	57
Boys	13-15 years	47.8	2450	70
Girls	13-15 years	46.7	2060	65
Boys	16-18 years	57	2640	78
Girls	16-18 years	50	2060	63

almonds form a part of the spice mixture added to vegetable gravies. In Punjab, milk and milk products like curds (yogurt), paneer (kind of cheese that is not fermented) and buttermilk are consumed as such or added to vegetables or sweets may be prepared using these.

In the eastern part of India, fresh water fish and rice forms the staple diet. Barley is another cereal commonly consumed here. Vegetables are again eaten as chutneys or salads or as gravies. Here too milk and milk products may be consumed as such or they could be added to gravies or turned into desserts. The oil used for cooking is mustard oil and palm jaggery is used in cooking as well as for making sweets. Meat is also consumed.

In the southern states, rice is the main cereal. Ragi (finger millet, small brown seeds which look like mustard seeds are rich sources of calcium) is also eaten by people from low and high income levels. Kerela is one of the southern states which has a long coastline, thus fish, fresh coconut and coconut oil are used extensively in the daily diet. Fermented cereal and pulse products like idlis, dosas, appams are consumed everyday at breakfast and snack times. Groundnut and sesame oils are used in the cooking in the state of Tamil Nadu.

In the western part of the country, wheat, rice, jowar (Sorghum), bajara (pearl millet) and ragi are the main cereals consumed. These are eaten with dals or vegetable gravies or with meat, fish (coastal parts of Maharashtra and in Goa) or chicken. Oil used is groundnut oil. In the coastal regions again fresh coconut is used in daily cooking.

Basic Five Food Groups: Recommended by the National Institute of Nutrition (NIN), Hyderabad

- *Food Group I:* Cereal grains and their products
- *Food Group II:* Pulses and legumes, nuts and oilseeds
- *Food Group III:* Milk, meat, fish, chicken and eggs and their Products
- *Food Group IV:* Fruits and vegetables (sub divided into fruits, leafy vegetables and other vegetables)
- *Food Group V:* Subdivided into fats and oils; sugar and jaggery.

Interaction between HIV/AIDS and Nutrition

HIV progresses more rapidly in poorly nourished individuals, which become a vicious cycle resulting in untimely death. HIV results in malnutrition with associated micronutrient deficiencies, loss of lean body tissue as a part of the disease process and a reduced food intake, chronic diarrhea or malabsorption in addition to increased nutritional requirements.[13,29]

There is a significant interaction between HIV/ AIDS, nutrition status and immune function. Severe malnutrition results in an impaired immune function increasing the risk of opportunistic infections. Micronutrient deficiencies are common which may lead to the accelerated progression of the disease.[5]

Malnutrition amongst children with HIV/AIDS impacts on morbidity and mortality, with an estimated 56 percent of deaths as a consequence of malnutrition; it is a significant clinical prognostic marker. The successful management of malnutrition impacts/improves the quality of life.[5]

A good nutrition status delays disease progression and the introduction of ARVs. However, nutrition status must be maintained with ARVs in order to increase the efficacy of the medications prescribed. Where children are not gaining weight even after therapy has been instituted, a thorough clinical workup for concurrent opportunistic infections such as tuberculosis should be sought.[29] HIV infected women and children under the age of 5 years, are the most vulnerable within a population and should be actively targeted to undergo regular nutrition screening in order to determine nutrition risk allowing for timely nutrition support to be implemented.[1-3]

Household Food Security

In order for malnutrition to be alleviated the United Nations identified the following factors: sufficient household food security allowing for the promotion of a healthy diet, sufficient psychosocial support within a family unit, adequate health services and a safe environment.[29]

Household food security is linked to the prevalence of HIV/AIDS within countries and the ability of communities or family units to remain economically active. The epidemic has resulted in fewer economically active household members in addition to a rise in the number of dependents increasing the burden of care amongst those remaining. Amongst the remaining adults in a family there is often a decrease or loss of assets increasing the risk of hunger and malnutrition.[29]

There is also a significant change in the dependency patterns across regions affected by the HIV epidemic relative to the increasing number of orphans (up to 13% of all children having lost either mother or both parents) and the increased burden relative to caring for sick adults. Of this figure, 50 percent is as a result of HIV/AIDS. The effect of this loss is that households are less able to adapt to finding work related activities, which include planning strategies to make ends meet or gathering of wild foods and the ability to prepare these foods.[29]

HIV infection is associated with an increase in resting energy expenditure (REE), which could be related to the HIV infection itself or other opportunistic infections, fever and or cytokine release.[30] Additional calories should be provided to HIV infected children with the aim of maintaining nutrition status and promoting growth. Once nutrition rehabilitation has occurred a review of dietary recommendations should occur to ensure that children receiving ARVs do not develop comorbid complications such as obesity.[19]

Diet History

At each review it is important to establish a diet history and whether anything has changed since the last visit. (Table 5.1.11) can be used as a rough guide to meal and milk frequency.

Table 5.1.11: Dietary history questions[1]

Under the age of 1 year	*Over the age of 1 year*
1. ***If the mother is breastfeeding***	***Ability to eat***
• How many times per day is the child drinking from the breast?	• How many meals a day does the child eat?
If mother is bottle feeding?	• How much at one meal does he eat?
• How many bottles is she giving per 24 hours?	• What kinds of foods does he eat?
• How many ml of infant feed per bottle?	• How often are protein rich foods eaten?
• How many scoops of feed per how many ml of water?	• How often is fruit eaten?
• What water is being used to prepare the milk, e.g. boiled cooled or hot?	• Is anything 'extra' added to the complementary foods?
	• Does the child drink milk?
• How many bottles are made at a time?	• How much?
• How long does the child drink from the bottle?	• Does the child drink other fluids–what and how much?
• What type of milk feed is she giving?	• Does the child have snacks in between meals–what and how much?
2. ***Complimentary foods***	• Does the caregiver perceive the child is eating well?
• At what age were complimentary feeds introduced?	• Does the child appear to have any difficulties with eating?
• What is being given, how much, how often?	• Does the child have increased requirements due to chronic lung disease or LIP?
• Does the caregiver perceive the child is eating well?	
• Is anything 'extra' added to the complementary foods?	• Has the child previously received nutrition supplements?
• Intake of other fluids; water, tea, juice?	• Is the child currently receiving nutrition supplements?
• Does the child appear to have any difficulties with eating?	

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Commonly used Drugs in Management of HIV/AIDS

ARV medication currently used commonly can be divided into three classes; nucleoside reverse transcriptase inhibitors (NRTI), non nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI). Usually, they are given in combination and can interact with food and other drugs and are known to cause numerous side effects. Table 5.1.12 provides a summary of some drug nutrient interactions. In brief PIs often cause diarrhea and nausea, NRTIs cause headaches, nausea, anaemia and fatigue and NNRTIs can result in central nervous system changes.[5]

Many of the drugs used to treat opportunistic infections have overlapping toxicities with ARV drugs. Metabolic effects of ARVs are most commonly associated with protease inhibitors (PIs) but may also be seen in

Table 5.1.12: Potential drug-nutrient interactions resulting in weight loss and malnutrition

Medication on empty stomach	*Purpose*	*Recommended to be taken*	*Potential side effects*
Rifampin	Treatment of tuberculosis	On an empty stomach one hour before or two hours after meals. Avoid alcohol	Nausea, vomiting, diarrhea and loss of appetite
Isoniazid	Treatment of tuberculosis	One hour before or two hours after meals. Avoid alcohol. May cause possible reactions with foods such as bananas, beer, avocados, liver, smoked pickled fish, yeast and yoghurt	Anorexia and diarrhea, may interfere with Vitamin B6 metabolism, therefore, may require Vitamin B6 supplement
Zidovudine	Antiretroviral NA	30 minutes before meals/1 hour after meals Avoid alcohol	Megaloblastic anemia, anorexia, nausea, vomiting and diarrhea, sweat, flu-like symptoms, increased triglycerides, dysguesia, edema of tongue and lips, mouth ulcers, constipation
Didanosine	Antiretroviral NA	On empty stomach, drink fluids frequently, do not take antacids simultaneously	GI symptoms, diarrhea, hepatomegaly, pancreatitis, hepatitis, headache, malaise, edema, dehydration
With Food			
Lamivudine	Antiretroviral NA	With food/on empty stomach	GI symptoms
Flucanozole	Treatment of candida	With food	Nausea, vomiting, diarrhea. Can be used when breastfeeding.
Nystatin	Treatment of thrush	With food	Infrequent occurrence of diarrhea, vomiting, nausea
Zidovidune/Lamivudine	Antiretroviral combination NA	With food Avoid alcohol	Nausea, vomiting, abdominal cramps, diarrhea
Stavudine	Antiretroviral NA	With food	Peripheral neuropathy, hepatitis, pancreatitis, lactic acidosis, fever, chills
Nevirapine	Antiretroviral NNRTI	With food	Sedative effect, diarrhea, nausea, and rash
Ritonavir	Antiretroviral PI	With food, suck ice to dull tastebuds, give strong-flavoured chewing gum immediately after dose. Garlic in large amounts impairs pharmokinetics	GI symptoms, headache, rash, sweat, taste disorders, pharyngitis, cough, hyperlipidemia, may impair growth in children
Efavirenz	Antiretroviral NNRTI	Not with fatty meal, take at bedtime.	GI symptoms, taste disorders, skin rash

NA = Nucleoside analogs, PI = Protease inhibitors, NNRTI = Non-nucleoside reverse transcriptase inhibitors

children taking nonnucleoside reverse transcriptase inhibitors (NNRTIs) and nucleoside reverse transcriptase inhibitors (NRTIs). Most common metabolic effects are lipoatrophy (subcutaneous fat wasting), lipohypertrophy (regional fat accumulation), insulin resistance, hyperlipidemia and lactic acidemia. The more malnourished the child is on commencing ARVs the more likely to develop metabolic problems and as such should be carefully monitored.[19]

Pediatric ARV solutions generally use either a non-absorbable sugar or sugar within the syrup, e.g. lactulose, sorbitol or sucrose. If a child has chronic osmotic diarrhea ARV syrups may exacerbate the condition. The child should be referred to a level 2 or 3 center for further medical management.

Nutrition Management

The Chart Book and Handbook of Guidelines for an Integrated Approach to Nutrition Care should be used to define and determine an appropriate nutrition intervention around one of the 3 care plans, e.g. Nutrition Care Plan A, B or C (Appendix 5.1.1). The promotion of food-based options is available in Nutrition Care Plan A and food choices with defined calorie and protein content are outlined in Tables 5.1.13A to C. Where children require a more therapeutic nutrition intervention, the use of Ready to Use Therapeutic Food (RTUF) should be considered based on the WHO Moderate and Severe Malnutrition guidelines. RTUF is preferred, as the paste is less likely to become bacterially contaminated when compared to a similar liquid alternative, e.g. F100.[25,31-33]

The Indian diet is predominately cereal based.

Table 5.1.13A: Classification of food choices based on their calorie contents

Sr.no	Food	Amount (gm)	Energy (Kcal)	Proteins (gm)
Foods giving >50 kcal				
1.	Peanuts (roasted)	10	57	2.6
2.	Dry coconut	10	66	0.7
3.	Sesame	10	56	1.8
4.	Banana	100	116	-
5.	Sweet potato	50	60	-
6.	Tapioca	50	80	-
Foods giving 30-50 Kcal				
7.	Fresh coconut	10	44	0.4
8.	Bengal gram dal	10	37	2.1
9.	Bengal gram flour	10	37	2.1
10.	Roasted bengal gram	10	37	2.2
11.	Green gram dal	10	35	2.4
12.	Black gram dal	10	35	2.4
13.	Ghee/clarified butter	5	45	-
14.	Oil	5	45	-
15.	Dried dates	10	31	-
16.	Raisins	10	31	-
17.	Potato	50	50	-
18.	Yam	50	50	-
19.	Colocasia root	50	50	-
Foods giving less than 25 Kcal				
20.	Milk powder(whole)	5	25	1.3
21.	Sugar/jaggery	5	20	-
22.	Soyabean flour	5	21	2.1
23.	Arrowroot flour	5	16	-
24.	Sago/sago flour	5	17	-
25.	Paneer/cottage cheese	5	15	0.7

Table 5.1.13B: Common Indian recipes and snack items with defined calorie and protein contents

Common Indian recipes breakfast or snack items	Amount	Energy (Kcal)	Protein (gm)
Idli with coconut chutney	2 no with 2 tsps	294	7.4
Masala dosa with chutney and sambar	1 med; 2tsp chutney; 100 ml sambar	418	10
Wada-pav	1 pav and 75 gm wada	259	5.5
Sabudana Khichdi	100-125 g	324	5.2
Lapshi (sweet)	125-150 g	220	5
Lapshi Upma	125-150 gm	207	4
Sheera	100 gm	250	3
Bread-butter	2 slices with 2 tsp butter	177	4
Egg	1 boiled	67	6.7
Cornflakes with sugar and milk	200 gm	270	8
Besan or any other ladoo	30-40 gm	420	8
Peanut or any other nut chikki	20-30 gm	240	6.5
Vegetable sandwich	2 slices bread	191	4
Bhel-puri	100 gm	254	7
Chivda	75 gm	283	4.6
Chakli	50 gm	230	6
Milk	150 ml	150	6

Contd...

Contd...

Curds	150 gm	150	6
paneer	50 gm	132	6
Items in lunch or dinner			
Chapatis	1 big/1 med	290/163	7.2/3.6
Paratha/Paratha stuffed	1 big/With potato 1 big	290/390	7.2/7.2
Bhakri	1 med	100	2-3
Puris	5 med	190	4
Rice	30 g raw rice = 1 katori cooked	100	2
Vegetable pulav	30 gms rice; 50 gm vegetables	200	1.2
Rice-dal khichdi	100 gm	195	5
Chicken curry with coconut	100 gm	110	13.6
Meat	100 gm	110	12
Fish fry	2 pieces	135	8.8
Fish curry	100 gm	133	8.8
Salad	50-75 gm	30-50	-
Any legume usal	125-150 gm	189	6
Dal made from any pulse	125-150 gm	145	6
Any vegetable preparation	125-150 gm	75-100	1-2
Dahi-boondi	100	162	4
Papad	1 med roasted/med fried	34/52	2/2
Kadhi	150 ml	125	4
Waran	150 ml	136	6
Kheer made with milk and any cereal/pulse	150 ml	262	8

Table 5.1.13C: Classification of food choices based on calorie contents <50 Kcal, 50-100 Kcal, 100-150 Kcal and 7600 Kcal

Food item	*Amount*	*Energy (kcal)*	*Protein (g)*	*Food item*	*Amount*	*Energy (kcal)*	*Protein (g)*
			< 50 Kcal				
1 teaspoon fish paste	5 g	9	0.75	1 teaspoon peanut butter	5 g	29	1.2
1 teaspoon jam	5 g	13	0	2 teaspoons sugar	10 g	30	0
1 teaspoon cheese spread	5 g	15	0.8	Cheese	10 g	35	2
2 teaspoons fish paste	10 g	18	1.5	1 teaspoon margarine	5ml/g	36	0
1 teaspoons sugar	5 g	19	0	1 teaspoon oil	5 ml	44	0
2 teaspoon jam	10 g	26	0				
			50-100 Kcal				
2 teaspoon peanut butter	10 g	58	2.4	2 teaspoons oil	10 ml	88	0
Pumpkin, sugar, oil (1/2 small bowl)	50 g	62	0.5	Egg, boiled	60 g	88	7.6
2 teaspoons margarine	10 g/ml	72	0	Raisins (handful)	27 g	88	0.86
Orange Juice	200 ml	94	1.4	Banana, med to large	100 g	92	1.3
			100-150 Kcal				
Milk, Low fat	200 ml	102	6.4	Meat ball, small	60 g	125	16
Egg, scrambled with milk	60 g	105	6.2	Milk, full cream	200 ml	125	6.4
Apple Juice	200 ml	106	0.2	Maas / sour milk	200 ml	129	6.6
Chicken, drumstick	42 g	106	10.9	Banana, fried in sunflower oil med-large	100 g	131	0.9
Onions, fried in oil (2 tablespoons)	50 g	107	0.65	Sugar beans (1/2 cup)	125 g	116	6
Egg, fried	60 g	109	7.5				

Contd...

150-200 Kcal							
Fruit yoghurt, low fat Avocado, half	175 ml 75 g	157 183	6.7 0.98	Yoghurt, full cream	175 ml	180	7.7
200-250 kcal							
Peanut or other nut butter chappati	1 small	215	7.6	Meat patty, medium	80 g	228	21.6
250-300 Kcal							
Peanut or other nuts (1/2 cup)	50 g	291	13.2				
300-350 Kcal							
Buttermilk/sour milk	500 ml	305	17.5	Bread with margarine and peanut butter	1 slice	321	8.1
350-400 Kcal							
Roti/Chapati	60 g	357	2.7				
400-500 kcal				500-600 kcal			
Egg mayonnaise sandwich and yoghurt	2 slices & 175 ml	406	19.3	Cheese and tomato sandwiches x 2	4 slices	520	24
> 600 Kcal							
Peanut (1 cup) Milk/maas full cream and 4 tablespoons full cream milk powder	100 g 500 ml	582 605	26.2 30.7	Maas, sour milk Roti x 2	1 l 120 g	605 704	35 g 5.4

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An Indian meal generally comprises of cereal or cereal products, consumed along with legumes or pulses, vegetables, nonvegetarian foods and milk and milk products.

Other components of the meal are pickles made from a variety of fruits and vegetables, chutneys and papads.

An Indian meal can be made calorie dense by:

1. Adding the following ingredients while cooking food. These ingredients can be added in the gravies, as (Table. 5.1.13A) a part of salad or as a garnish.
2. Certain snack time foods that are home made and easy to prepare, yet energy dense can be incorporated to add calories. Some of these are laddoos, chivda, farsan, sev, roasted peanuts, roasted bengal gram dal, parched or puffed cereals, chikki, shakkarparas, murruku, sukhadi, golpapdi.
3. In most households with limited income, pickles, chutneys and papads, substitute vegetables and pulses, contributing to the calorie content of a meal. Dry chutneys prepared from different pulses, nuts or oilseeds like bengal gram (chana dal), green gram (mung dal), black gram (udid dal), peanuts, fresh or dry coconut, sesame, flaxseeds can be used. Papads are dehydrated food made from pulses or cereals. These can be deep fried or roasted to give a crisp product like potato chips. Similarly, fried chips made from banana, jackfruit or potatoes also increase the energy content of the meal.

Coping with the Nutrition Complications of HIV/AIDS

During the course of the disease, children may experience some of the common symptoms related to HIV/AIDS. Suggestions in Table 5.1.14 provide a guide as to which foods should be eaten or avoided for the following symptoms:[1]

- Diarrhea
- Lack of appetite
- Nausea and vomiting
- Sore mouth or when eating is painful
- Other digestive problems
- Changes in the taste of food
- Skin problems
- Fever

In addition to this, the WHO Integrated Nutrition Care of HIV infected children contain suggestion sheets on how to improve food intake.

Table 5.1.14: Practical suggestions on how to maximize food intake during and following common HIV/AIDS related symptoms[1]

Symptom	*Suggested strategy*
Fever and loss of appetite	• Drink high-energy, high protein liquids, fruit juice, vegetable and chicken soup and avoid strong smelling foods • Eat small portions of soft, preferred foods throughout the day using favorite foods and nutritious snacks whenever possible • Drink liquids often and beyond usual thirst • Bathe in cool water and rest • For fever take aspirin or paracetamol with a meal three times a day (morning, afternoon and evening) if available • Go to the healthcentre/ clinic in the case of: - Fever that lasts several days and is not relieved by aspirin - Loss of consciousness - Severe body pain - Yellow eyes - Severe diarrhea - Fits
Sore mouth and throat (Thrush)	• Avoid citrus fruits, tomato and spicy, salty and sour or sticky foods as they may irritate mouth ulcers. Avoid very sweet foods • Drink high-energy, high protein liquids with a straw • Eat foods at room temperature or cooler • Eat smooth foods such as puddings, porridge, mashed potato, mashed carrots or other nonacidic vegetables and fruits • Seek medical attention for treatment • If available, use a spoon or a cup to eat small quantities of food • Tilt head backwards when eating to assist with swallowing • Rinse mouth with boiled warm water after eating to help reduce the irritation and keep the infected areas clean so that yeast cannot grow. Drink plenty of clean, safe liquids
Nausea and vomiting	• Eat small snacks throughout the day and avoid large meals • Eat small and frequently - having an empty stomach worsens nausea • Avoid lying down after having eating wait at least 20 minutes in order to avoid vomiting • Lightly salted and dry foods may help to calm the stomach • Rest between meals • Eat dry biscuits, toast, bread and other plain dry foods • Avoid foods that have a strong flavor and smell • Drink diluted fruit juices, other liquids and soup • Eat simple boiled foods, such as porridge, potatoes, and beans • Avoid drinking liquids immediately after meals
Diarrhea	• Drink lots of fluids to avoid dehydration (soups, diluted fruit juices, boiled water) • Drink juices such as passion fruit, avoid strong citrus (orange & lemon) as it may irritate the stomach - dilute • Eat starchy foods like maize, rice and potato, including some of rice, potato water in the meal. • Boil or steam foods, avoid fried foods • Eat soft fruits and vegetable such as bananas, squash, mashed sweet potato or mashed carrots. • Avoid caffeine (coffee, tea and cool drinks, e.g. coke) • Eat smaller meals, more often • Limit gas-forming food such as cabbage, onions, carbonated soft drinks (sodas) • Eliminate dairy products to see if they are the cause. Decrease foods, which are high fat • Do not eat foods with insoluble fiber (roughage), e.g. fruit skins • Drink oral rehydration solution if diarrhea is severe
Fat malabsorption	• Eliminate oils, butter, margarine and foods that contain or were prepared with them • Eat only lean meats • Eat fruits, vegetables or other low fat foods

Contd...

7 years to adults

- Enjoy a variety of foods
- Be active
- Make starchy foods the basis of most meals
- Eat plenty of vegetables and fruits everyday
- Eat dry beans, peas, lentils and soy regularly
- Chicken, fish, milk, meat or eggs could be eaten daily
- Eat fats sparingly
- Use salt sparingly
- Drink lots of clean, safe water
- Use food and drinks containing sugar sparingly and not between meals.

Conclusion

HIV infected children should receive regular growth monitoring with healthcare workers adopting a low threshold for implementing nutrition support at the first signs of a child not growing well, whilst implementing appropriate concurrent medical management.

A good nutrition status in HIV infected children is important with respect to delaying disease progression and decreasing morbidity and mortality from opportunistic infections associated with malnutrition. An integrated approach to the nutrition management of HIV infected children as described in the WHO Guidelines provides a systematic approach to screening and implementation of a nutrition care plan with an exit strategy once the goals have been achieved.

APPENDIX-5.1.1

Key messages from the Guidelines to an Integrated Approach to the Nutrition Management of HIV infected children (6 months to 14 years).

This chapter on nutrition in HIV infected children should be read in conjunction with

1. *Guidelines for an integrated approach to the nutritional care of HIV infected children (6 month to 14 years). Preliminary Version for Country Introduction. Chart Booklet ISBN 978-924-15975-24 WHO Library Catalogue in Publication Data.*
2. *Guidelines for an integrated approach to the nutritional care of HIV infected children (6 months to 14 years). Local Adaptation ISBN 978-924-159752-4 WHO Library Catalogue in Publication Data ISBN 978-924-159752-4 WHO Library Catalogue in Publication Data.*
3. *Guidelines for an integrated approach to the nutritional care of HIV infected children (6 months to 14 years). Preliminary Version for Country Introduction. Handbook ISBN 978-924-159752-4 WHO Library Catalogue in Publication Data.*

Step 1: Assess, classify and decide on a nutrition care plan

- Regular growth monitoring (Step 8) helps to identify disease progression allowing for early intervention.

Step 2: Assess the child's nutritional needs

- The nutrition needs of a child will depend on growth pattern, stage of disease and whether there is a recent history of opportunistic infections or chronic diarrhea.

Step 3: Decide a nutrition care plan

Use the screening tool below to decide on a nutrition care plan for the child.

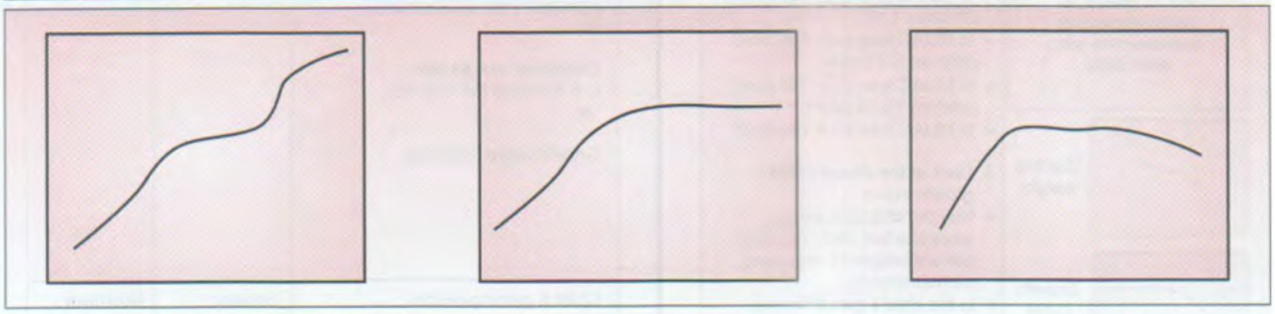
- Nutrition care plans have been split into A, B and C to give guidance as to nutrition support required to optimize nutrition status.
- Nutrition requirements vary according to the stage of disease which is taken into account in the three nutrition care plans.

Step 1: Assess and classify child's weight and growth

Ask	Look and feel
Ask mother/caregiver (or check the medical records) 1. Has the child lost weight during the past month?	1. Look for signs of severe visible wasting • Loss of muscle bulk • Sagging skin buttocks 2. Check for presence of edema of both feet (or sacrum) 3. Check the weight and height • Is the weight-for-height less than -3 Z-scores? • Is the child very low weight (weight-for-age less than -3 Z-scores)? • Is the child underweight (less than -2 Z-scores)? 4. Check the MUAC In infants 6-12 months • Is MUAC less than 115 mm? In children 13-60 months • Is MUAC less than 115 mm? In children 5-9 years • Is MUAC less than 135 mm? In children 10-14 years • Is MUAC less than 160 mm? 5. Look at the shape of the growth curve • Has the child lost weight since the last visit? (confirm current weight by repeating measurement) • Is the child's growth curve flattening? • Is the child gaining weight?

Assess growth in all children →

Signs	Classify as
Signs of severe visible wasting, or edema present in both feet, or weight-for-height less than -3 Z-scores below median WHO reference value, or MUAC less than: • 110 mm in infants 6-12 months • 110 mm in children 1-5 years • 135 mm in children 6-9 years* • 160 mm in children 10-14 years	Severe malnutrition
Reported weight loss, or Very low weight (weight-for-age less than-3 Z-scores), or Underweight (weight-for-age less than-2 Z-scores), or Confirmed weight loss (>5 %) since the last visit or Growth curve flattening	Poor weight gain
Child is gaining weight	Growing appropriately



Examples of growing well, curve flattening (crossing growth lines) and losing weight

Step 2: Assess the child's nutritional needs

Ask	Look and feel
Ask mother/caregiver (or check the medical records) Does the child have: • cough for more than 21 days? (this may be due to HIV-related chronic lung disease such as LIP or bronchiectasis) • active TB, i.e. on treatment • diarrhea for more than 14 days • other chronic OI or malignancy	At clinical sites decide if any of the following are present (check medical notes) • chronic lung disease, including LIP, bronchiectasis • active TB • persistent diarrhea

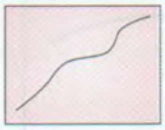
If Yes →

Signs	Classify as
Chronic lung disease, or TB, or persistent diarrhea, or other chronic OI or malignancy	Condition with increased nutritional needs

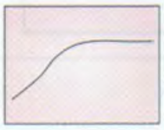
Note: Chronic lung disease is different from cough or difficult that has started recently

Ask	Look and feel
Ask mother/caregiver (or check the medical records- 1. Has the child lost weight during the past month ? 2. Does the child have: • Cough for more than 21 days (this may be due to HIV-related chronic lung disease such as LIP or bronchiectasis • Active TB on treatment • Diarrhea for more than 14 days • Other chronic OI or malignancy	1. Look for signs of severe visible wasting • Loss of muscle bulk • Sagging skin buttocks 2. Check for presence of oedema of both feet (or sacrum) 3. Check the weight and height • Is the weight-for-height less than 3 Z-scores? • Is the child very low weight (weight-for-age less than-3 Z-scores)? • Is the child underweight (weight-for-age less than -2 Z-scores)? 4. Check the MUAC Infants 6-12 months • Is MUAC less than 115 mm? Children 13-60 months • Is MUAC less than 115 mm? children 5-9 years • Is MUAC less than 135 mm? children 10-14 years • Is MUAC less than 160 mm? 5. Look at the shape of the growth curve • Has the child lost weight since the last visit? (confirm current weight by repeating measurement) • Is the child's growth curve flattening • Is the child gaining weight?

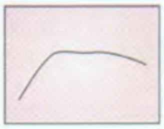
Ask all questions and complete all assessments with each child



Gaining weight



Growth curve flattening



Losing weight

Assess growth in all children →

Signs	Classify as	Treat
Signs of severe visible wasting, or edema present in both feet, or weight-for-height less than-3 Z-scores, or MU AC less than: • 115 mm in infants 6-12 months • 115 mm in children 13-60 years • 135 mm in children 5-9 years • 160 mm in children 10-14 years	Severe malnutrition	**Nutrition care plan C**
Reported weight loss, or Very low weight (weight-for -age less than -3 Z-scores), or Underweight (weight-for-age less than -2 Z-scores), or Confirmed weight loss (>5 %) since the last visit, or Growth curve flattening	Poor weight gain	**Nutrition care plan B**
Child is gaining weight	Growing appropriately	**Nutrition care plan A**
Chronic lung disease, or TB, or Persistent diarrhea, or other chronic OI or malignancy	Condition with increased nutritional needs	**Nutrition care plan B**

Set targets for energy and micronutrient intakes

Children that are growing well and asymptomatic or with mild symptoms only; (This may include children on ART >6 months following recovery of weight)

The energy needs of these children are increased by about 10 percent (based on actual weight rather than expected weight for age). The child still needs his/her age and weight specific energy intake. The additional energy helps to maintain normal growth, development, activity and body functions. The additional energy is best given through additional household foods, provided as part of a balanced, varied diet. If there is inadequate food for the child's entire household then *Family Food Support* may be required (Step 6)

Children with conditions with increased energy needs, e.g. chronic lung disease or chronic infections, e.g. TB or persistent diarrhea. Children may, or may not be, on ART.

Children with chronic illnesses may require an extra 20-30 percent energy each day (based on actual weight rather than expected weight for age). These children probably also need ART and should be referred to a treatment site for assessment and exclusion of TB. The additional 20-30 percent energy is best given through additional household foods, provided as part of a balanced, varied diet. If this is not possible, then specific ***nutritional supplements*** should be offered until the underlying causes of poor weight gain, or causes of additional energy needs, e.g. chronic lung disease, TB or HIV-related malignancy are effectively managed

Children with severe malnutrition, i.e. signs of visible wasting, bilateral edema or severely impaired growth. Children may, or may not be, on ART.

These children need 50-100 percent extra energy each day (based on actual weight rather than expected weight for age) for a limited period until weight is recovered. These children should be treated with ***therapeutic feeding*** which should continue until nutritional recovery is achieved (average - 6-10 weeks). They should also be referred to a ART treatment site for assessment and exclusion of TB.

Several malnourished infants with no medical complications can often be managed at home if they still have a good appetite. Children with a poor appetite, implying complications, should be referred for inpatient care. The nutritional management of HIV infected severely malnourished children is largely the same as for children without HIV infection except that they should also be assessed for ART. Other opportunistic infections such as thrush, TB or cryptosporidiosis should also be excluded and treated.

The presence or absence of appetite, i.e. no medical complications determines if the child can be managed at home or needs admission to hospital

Total energy needs of HIV infected children (Kcal/day)

	*Daily energy needs of HIV uninfected children**	*HIV infected and asymptomatic 10% additional energy*	*HIV infected and poor weight gain or other symptoms 20% additional energy*	*Severely malnourished and HIV infected (post-stabilisation) 50-100% additional energy***
6-11 months	690	760	830	150-220 kcal/kg/day
12-23 months	900	990	1080	150-220 kcal/kg/day
24-59 months	1260	1390	1510	150-220 kcal/kg/day
6-9 years	1650	1815	1980	75-100 kcal/kg/day
10-14 years	2020	2220	2420	60-90 kcal/kg/day

*Based on average of total energy requirements for light and moderate habitual physical activity levels for girls and boys by age group. Joint FAO/WHO/UNU Expert Consultation, October 2001. Fip:http.foo.org/docreplfoo/007ly568sety5686e00.pdf

** Management of severe malnutrition: a manual for physicians and other senior health workers. WHO, 1999.

Nutrition Care Plan A for the Child who is Growing well ± ART

1st Action. Ask about general condition and if child is on any treatment including Art and TB medicine?
- Also check immunization (step 7)
- Is the child at school?
- If child is on ART then also complete Step 10. Check if ART dose needs to be adjusted up.

2nd Action. Check mother's health (+ need for ART) and care of other children

3rd Action. Nutrition counseling
- Encourage mother/caregiver in indicating that the child is growing well. Explain growth chart and how to follow progress
- Ask, have there been any major changes in the child's circumstances from the last visit that might put the care of the child at risk, including access to food?
- Advise mother/care giver why additional food (energy) is needed in children (and adults) with HIV infection (approx 10%)
- Counsel on continued breastfeeding if mother is well (check national guidelines related to breastfeeding policy and age of the child)
- Counsel on complementary feeding and replacement feeding (frequency of meals, amount and type of food per meal, responsive feed). Reinforce and encourage good practices
- Counsel on feeding a variety of foods such as milk, fruit, vegetables, whole grains, cereals and meat/chicken or fish based on local diets, i.e. food sources that are high in vitamin A, iron, calcium, etc. and other locally produced foods
- Review safe food preparation, food and water storage methods and hygiene issues (keep hands, utensil and food preparation area clean; separate raw and cooked foods; cook food thoroughly; keep food at safe temperature; use safe water and food)
- Check if there are other sources of good foods such as garden projects or other community resources

4th action. Meet age specific needs and additional 10 percent energy based on acutal weight.

Examples of ways to increase energy intake by 10 percent using food
Give an addition to the meals and snacks appropriate for the child's age

6-11 months (additional 60-75 kcal = Total ~ 760 kcal/day)
- Local Adaptation – Give examples and quantities of local foods that can be used to increase energy density of other foods, e.g. 2 tsp margarine/oil and 1-2 tsp sugar to porridge of that can be given in addition to normal diet
- Examples of other switches in Table 5.1.13

12-23 months (additional 80-95 kcal = Total ~ 990 kcal/day)
- Local Adaptation – Give examples and quantities of local foods that can be used to increase energy density of other foods, e.g. margarine/oil and sugar to porridge or that can be given in addition to normal diet
- Examples of other switches in Table 5.1.13.

2-5 years (additional 100-140 kcal = Total ~ 1390 kcal/day)
- Local Adaptation – Give examples and quantities of local foods that can be used to increase energy density of other foods or that can be given in addition to normal diet, e.g. extra cup of full cream milk/fermented milk
- Examples of other switches in Table 5.1.13

6-9 years (additional 130-190 kcal = Total ~ 1815 kcal/day)
- Local Adaptation – Give examples and qualities of local foods that can be used to increase energy density of other foods or that can be given in addition to normal diet, e.g. extra cup of full cream milk/fermented milk
- Examples of other switches in Table 5.1.13

10-14 years (additional 170-230 kcal = Total ~ 2200 kcal/day)
- Local Adaptation – Give examples and quantities of local foods that can be used to increase energy density of other foods or that can be given in addition to normal diet, e.g. extra cup of fruit yoghurt or cheese/peanut butter sandwich
- Examples of other switches in Table 5.1.13

5th Action. Ensure adequate micronutrient intake
- If the child's diet is not balanced and does not contain a variety of animal sourced foods, fruits and vegetables, then give a daily micronutrient supplement that provides recommended daily allowance of a wide range of vitamins and other micronutrients. Refer to national guidelines.

6th Action. Vitamin A supplements every 6 months
- <6 months 50,000 IU 6-12 months 100,000 IU 1-5 years 200,000 IU

Do not give if child has received dose within the past month, e.g. from hospital

For children >5 years, vitamin A should be provided through regular daily micronutrient supplements

7th Action. De-worm every 6 month (Step 7)
- Albendazole (oral) 400 mg single dose every 6 months after first year of life.

8th Action. Contrimoxazole prophylaxis (Step 7)
- Provide from 6 weeks of age 5 mg/kg/day. See step 7 for guidance on when to stop.

9th Action. Ensure mother/caregiver understands care plan and ask if she/he has any questions

10th Action. Review in 2-3 months (tell caregiver to return earlier if problems arise)

Nutrition Care Plan B for the Child with Poor Weight Gain or Increased Nutritional Needs

1st Action. Clinically stage the child and assess for ART. Check for treatable conditions. If on ART, assess clinical and immunological response (complete step 10). Refer if indicated.

2nd Action. Check mother's health (+ need for ART) and care of other children

3rd Action. Nutrition counseling
- What does the child eat and drink? (Step 4)
- Who gives the child their food and how does the child eat? (Step 5)
- Is there food at home? (Step 6)
- Advise mother/care giver why additional food (energy) is needed in children (and adults) with HIV + complications
- Review safe food preparation, food and water storage methods and hygiene issues (Step 7)
- Ask, have there been any major changes in the child's circumstances from the last visit that might put the care of the child at risk, including access to food? (Step 6).

4th Action. Meet age-specific needs and additional 20-30 percent food (energy) based on actual weight
- *These needs may be achieved either through a food-based approach or through specific nutritional supplements—either form of support should be provided by service/program*

Food-based approach		**Nutritional supplement**
GIVE IN ADDITION TO MEALS AND SNACKS	OR	GIVE IN ADDITION TO MEALS AND SNACKS
6-11 months (additional 120-150 kcal per day)		6-11 months (additional 120-150 kcal per day)·
• Local Adaptation: Give examples of quantities and frequency of local foods that can be used to increase energy density of other foods, e.g. 2 tsp margarine/oil and 1-2 tsp sugar to porridge. Aim to add 3 times daily.	OR	• Local Adaptation to provide National or other recommendations
12-23 months (additional 160-190 kcal per day)		12-23 month (additional 160-190 kcal per day)
• Local Adaptation: Give examples of quantities and frequency of local food that can be used to increase energy density of other foods, e.g. extra cup of full cream milk or cheese/peanut butter sandwich (1 slice).	OR	• Local Adaptation to provide National or other recommendations
2-5 years (additional 200-280 kcal per day)		2-5 years (additional 200-280 kcal per day)
• Local Adaptation: Give examples of quantities and frequency of local foods that can be used to increase energy density of other foods, e.g. extra cup of enriched milk or cheese/peanut butter sandwich (4 slices).	OR	• Local Adaptation to provided National or other recommendations
6-9 years (additional 260-380 kcal per day)		6-9 years (additional 260-380 kcal per day)
• Local Adaptation: Give examples of quantities and frequency of local foods that can be used to increase energy density of other foods, e.g. extra cup of enriched milk of cheese/peanut butter sandwich (6 slices).	OR	• Local Adaptation to provide National or other recommendations
10-14 years (additional 340-400 kcal per day)		10-14 years (additional 340-400 kcal per day)
• Local Adaptation: Give examples of quantities and frequency of local foods that can be used to increase energy density of other foods, e.g. 3 cheese/peanut butter/egg sandwiches (8 slices).	OR	• Local Adaptation to provide National or other recommendations

See Table 5.1.13 for examples of foods or nutritional supplements that can provide additional 20-30 percent energy.

5th Action. Ensure adequate micronutrient intake
- If the child's diet is not balanced then give a daily micronutrients supplement that provides RDA of a wide range of vitamins and other micronutrients (refer to national guidelines)
- Check if any prescribed nutritional supplement provides micronutrient intake. Additional supplements may not be needed
- If recent diarrhoeal illness, gives zinc supplement (20 mg daily for 2 weeks)

6th Action. Vitamin A supplements every 6 months
- <6 months – 50,000 IU   6-12 months – 100,000 IU   >12 months – 200,000 IU

Do not give if child has received dose within the past month, e.g. from hospital

> For children >5 years, vitamin A should be provided through regular daily micronutrient supplement

7th Action. De-worm every 6 month (Step 7)
- Albendazole (oral) 400 mg single dose every 6 months after first year of life.

8th Action. Contrimoxazole prophylaxis (Step 7)
- Provide from 6 weeks of age 5 mg/kg/day. See step 7 for guidance on when to stop.

9th Action. Ensure mother/caregiver understands care plan and ask if she/he has any questions

10th Action. Review 1st visit 1-2 weeks. If responding, then review every 1-2 months depending on response. Change to Nutrition Care Plan A when nutritional recovery achieved.

Nutrition Care Plan C for the Severely Malnourished HIV Infected Child

1st Action. Assess if the child needs to be admitted ***CHECK FOR GENERAL DANGER SIGNS***

- Assess if there are signs of a concurrent opportunistic infection. If yes, then Admit and Treat accordingly
- Assess if the child wants to eat. Conduct a test feed (Step 4). If the child will not eat (suggestive of underlying complications) then refer to specialized care for management as per WHO management of children with severe malnutrition
- If the child eats well then plan home (community-based) management according to table below. Prescribe feeds
- Assess if there have been any major changes in the child's circumstances? (Step 5).

2nd Action. Clinically stage the child and assess for ART. Check for treatable conditions. If on ART, assess clinical and immunological response (complete Step 10). Refer if indicated.

- All severely malnourished children or those with recent severe weight loss should be assessed for possible ART and to exclude opportunistic infections such as TB

3rd Action. Check mother's health (+ need for ART) and care of other children.

4th Action. Home management. Give Therapeutic feeds to provide 50-100 percent additional energy

Give therapeutic feeding (average ~ 6-10 weeks)

Provide 60-220 kcal/kg/day depending on age (do not rely on home foods being available)

6-11 months (150-220 kcal/day based on actual weight)

- Local adaptation – WHO recommends providing RUTF as the *Therapeutic Feed* of choice to children that are severely malnourished in the recovery growth catch-up phase of management. National recommendations should be followed to provide the target energy intake by age group.

12-23 months (150-220 kcal/day based on actual weight)

- Local adaptation – WHO recommends providing RUTF as the *Therapeutic Feed* of choice to children that are severely malnourished in the recovery growth catch-up phase of management. National recommendations should be followed to provide the target energy intake by age group.

2-5 years (150-220 kcal/day based on actual weight)

- Local adaptation – WHO recommends providing RUTF as the *Therapeutic Feed* of choice to children that are severely malnourished in the recovery growth catch-up phase of management. National recommendations should be followed to provide the target energy intake by age group.

6-9 years (150-220 kcal/day based on actual weight)

- Local adaptation – WHO recommends providing RUTF as the *Therapeutic Feed* of choice to children that are severely malnourished in the recovery growth catch-up phase of management. National recommendations should be followed to provide the target energy intake by age group.

10-14 years (150-220 kcal/day based on actual weight)

- Local adaptation – WHO recommends providing RUTF as the *Therapeutic Feed* of choice to children that are severely malnourished in the recovery growth catch-up phase of management. National recommendations should be followed to provide the target energy intake by age group.

5th Action. Ensure adequate micronutrient intake

- A child receiving RUTF will receive all the micronutrients that they require through the feeds
- A child that receives the therapeutic feeding based on local foods is unlikely to receive all micronutrients in the required amounts and may therefore need a separate, additional vitamin-mineral supplement that meets defined standards. In addition, many commercial vitamin-mineral supplements do not contain adequate amounts of zinc and separate supplements of zinc may also be needed (see National guidelines)
- If recent diarrheal illness and child not receiving RUTF, give zinc supplement (20 mg daily for 2-4 weeks).

6th Action. Vitamin A supplements every 6 months

- <6 months – 50,000 IU   6-12 months – 100,000 IU   > 12 months – 200,000 IU

Do not give if child has received dose within the past month, e.g. from hospital

7th Action. De-worm every 6 month (Step 7)

- Albendazole (oral) 400 mg single dose every 6 months after first year of life

8th Action. Contrimoxazole prophylaxis (Step 7)

- Provide from 6 weeks of age 5 mg/kg/day. See step 7 for guidance on when to stop

9th Action. Ensure mother/caregiver understands care plan and ask if she/he has any questions

10th Action. If managed at home, then review 1 week to ensure weight gain of at least 5 g/kg/d. (if managed in hospital then would expect weight gain of ~ 5-15 g/kg/day). If gaining weight then review every 1-2 weeks until recovery (children can usually only tolerate this energy intake for 6-10 weeks). If not gaining weight then consider admission. Review and change to plan A or plan B if child has condition with increased nutritional needs.

- **Step 4: What does the child eat and drink?**

If a child is not growing well or there has been recent weight loss or growth faltering or the child is underweight, then check what the child eats and drinks.

Assess	*Classify/Consider*	*Counsel*
1. **Ask about milk given** • What types of milk do you usually give to the child each day? • How much, and how often do you give these? • Do you ever breastfeed your child?	If no solid food eaten in last 4 meals, or only milk taken in the last 24 hours then classify as Serious Poor Food intake	If serious Poor Food Intake then refer urgently for admission of other immediate social/welfare support
2. **Food intake (past 24 hours)** Ask, from the time the child woke up yesterday until he/she went to sleep at night, what did he/she eat: For breakfast For lunch As a snack between breakfast and lunch For dinner As a snack between lunch and dinner • Was the frequency of meals and snacks appropriate for the child's age? • Was the quantity of the main meal appropriate for the child's age? • Did the child eat meat, fish or eggs in the past week?	If food intake is less than recommended then classify as Poor Food intake. Try to identify cause, e.g. recent illness, change in social circumstances, and ask if this is because there is insufficient supply, reluctance to drink or unsure of correct volumes. If food intake adequate then classify as Food intake adequate	If Poor Food intake then • Counsel on complementary feeds • Also consider Food support (Step 6) if appropriate (check what other public sector support is available, e.g. grants and other NGO/CBO support in the area) • Assess and exclude other medical conditions If adequate and no changes in food intake then assess complementary feeding practices and then who feeds the child and how the child eats (Step 5).

Age-related milk and food intake standards	Appropriate		Insufficient
	Full cream milk (incl. fermented milks)	Food (cooked)*	Anything less than the recommended amount
6-11 months	If BF, then frequently/on demand		
12-23 months	If not BF, then 200-500 ml/day	½ cup × 4/day	
24-59 months	200-500 ml/day (2-3 cups)	¾ -1 cup × 4/day	
6-9 years	500-750 ml/day (2-3 cups)	1-2 cups × 4/day	
10-14 years	500-750 ml/day (2-3 cups)	2-3 cups × 3/day	
	* 1 cup = 240 ml	*1 cup = 240 ml	

If Food Intake is Insufficient then also Assess Ability to Eat

3. **Ability to eat (past 48 hour)** Ask, does the child • Vomit everything • Frequently vomit • Vomit occasionally • Have difficulty swallowing/chewing • Have mouth sores/ulcers • Eat well	If any difficulty is identified then assess if there is a problem of • Poor appetite • Sore mouth/throat • Change in taste • Vomiting • Other	If vomiting everything then refer urgently, check for dehydration Step 9 for guidance on children with specific needs If the child is on ART and vomiting – Step 10 for children on ART

- **Step 6. Assess if there is food shortage and financial support**

(local adaptations to these guidelines should include resources/response as appropriate)

Assess	*Classify*	*Manage*
1. **Financial Support available to caregiver** a. Does anyone in the household have regular income?	If yes, then classify as financially supported. If no, then classify as No financial support	If No financial support explore whether additional support might be helpful and whether referral to other services might be appropriate, e.g. social worker or child protection or other local community resources.(health worker needs to explore and know what other resources are available in the local communities)

Contd...

2. Food access (past 4 weeks) • Have there been days in the past 4 weeks when there has not been enough food available to feed the child? e.g. when you have had to skip meals yourself or for the child or give smaller amounts?	If the answers • Is yes, then classify as 'Serious food shortage'	If classified as **'Serious food shortage'** then refer **urgently** to local services for Family Food Support
If yes, then ask • Does this happen every week?	If the answer is yes, then classify as 'Food **shortage'**	If classified as **'Food shortage'** then refer to local services and other community resources for consideration of Family Food Support. Explore options for food gardens etc.

When to provide Family Food Support

- If **Serious Food shortage** is identified the **urgent** support must be found
- If **Food shortage** is identified then programs should explore ways of assisting the parent/caregiver which may include providing Food Support.

When to stop Family Food Support (consider combination of criteria):

- Until the acute circumstances have resolved, or
- Time-related, e.g. 6 months, or
- If the child is gaining weight and at least-1 Z-score for weight-for-height or weight-for-age. (Table 5.1.5)

Support for entire family/other children. Local policies will need to decide if they will support individual children/+siblings/+entire family.

Review

Condition	*Review interval*	*Comment*
The child who is well and growing appropriately	2-3 months	Unless needing to attend to receive routine cotrimoxazole/micronutrient or other support/ treatment
The child on ART	3 months 2-4 weeks	If gaining weight and no other problems If failing to gain weight
The child who has chronic increased nutritional needs but investigated and no other active problems	2-3 months	Tell caregiver to return earlier if problems arise
Child starting on Nutrition Care Plan B	First visit 1-2 weeks then 1-2 months	Tell caregiver to return earlier if problems arise
The child who is unwell and/or showing signs of growth faltering or has had recent diarrheal illness	2-4 weeks	May require more frequent visits depending on clinical status and support offered or being provided
When the child is malnourished +/- other signs of disease progression, e.g. history of recent severe weight loss or recent diarrhea illness	Weekly	Only if fulfils criteria for management at home and no other investigations immediately required that require hospitalization
When a child is severely malnourished or has *very low weight* and no explanation/diagnosis has been identified	Admit for investigation	

Nutrition Care Plan A, B or C

Within the Integrated Approach to Nutrition Care of HIV infected children, three nutrition care plans have been identified. The aim of these plans is to provide an entry or implementation strategy, a review process and exit phase when the goals of the initial plan are achieved.

The estimated energy requirements of an HIV infected child are provided with the text of the handbook.

Step 4: What does the child eat and drink?

- An essential part of any nutrition counseling is a thorough diet history which should include aspects

of what the child currently eats and the availability of food.

Step 5: Discuss who gives the child food and how the child eats ?

It is important to ascertain who feeds the child in addition to how well the child eats, especially if a mother has recently died and/or is too unwell to cook/ care for her children. If small children are left to fend for themselves and do not have an individual caregiver feeding them they may fail to take in sufficient food to meet their nutrition requirements.

Step 6: Assess if there is food and income at home

It is always important to consider the nutrition needs of the entire family as the sick child may have siblings that have not been brought into a clinic who are also HIV infected and or failing to grow well. Establish whether or not there is a financial support available to the family and whether there is sufficient access to food.

Step 7: Discuss exercise and avoid risk factors for malnutrition

Provide nutrition and medical interventions to prevent malnutrition, e.g. appropriate complementary feeding advice, referral to care agencies for additional financial / nutrition support, de worming, micronutrient supplementation, cotrimoxazole.

Step 8: Decide if to refer and when to review

Referral, review and follow-up are essential for all HIV infected children.

The Chart Book, Handbook and local adaptation are essential reading to providing an Integrated Nutrition Care Plan for HIV Infected children between the ages of 6 months to 14 years. They also contain suggestion sheets for a variety of aspects of nutrition care which impact on HIV infected children such as diarrhea, vomiting, cadidiasis amongst others.[1-3]

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5.2

Vaccinations for HIV Infected Children

Jacob T John

Introduction

As a consequence of immunodeficiency, HIV infected children are more susceptible to disease caused by infectious agents and are more likely to develop severe complications in comparison to immunocompetent children. HIV infection thus increases the need for vaccinations against all endemic vaccine-preventable diseases. At the same time, the success of vaccination depends on the individual's immune competence. Since, HIV infection causes immunodeficiency, it suppresses the immune responses to vaccination. For these reasons, in some situations the vaccination schedule may require modifications to improve and sustain immunity.

In infants who were infected prenatally with HIV, two practical factors come into play. One, immunosuppression would be minimal, if any, during the early weeks of life when most of the primary series of vaccines are either started or completed. Thus, it appears to be quite safe to follow the recommended normal schedule of vaccinations for infants even when the mother is known to be HIV infected. Even when antiretroviral treatment has not been given to the mother (and infant) to prevent mother-to-child transmission of HIV, it is prudent to recognize that the majority of infants are not infected under natural conditions. Therefore, in such instances the infant should be vaccinated as if uninfected.

Under standard health care practice, the determination of HIV infection status of the infant is delayed until about 18 months of age. Thus, unless the child had rapidly progressing HIV-related disease(s), usual "routine" vaccinations should be offered according to the age.

There may be situations when HIV infection is confirmed or strongly suspected before any or all of the doses of standard vaccines are given. This may be due to delays, either deliberately or by default. In such unlikely situations, more thought has to be exercised when vaccinating infants who may be considered HIV infected, although actual laboratory evidence can only be obtained later on.

All vaccines come under two broad categories—live attenuated and non-replicating. All live attenuated vaccines infect the host and multiply before inducing immunity. Even in fully immunocompetent children, some live vaccines may cause a very mild and incomplete form of disease that mimics the natural disease in some features. The risk of increased severity of such vaccine-induced disease is a cause for concern when HIV infected children are vaccinated. Thus, the risks and benefits of vaccinations should be carefully considered when caring for children with HIV infection.

HIV infection leads to immune deficiency mainly through the loss of CD4+ T lymphocytes that are essential for normal immune functions, while B lymphocytes are relatively unaffected at least in the early phase of HIV infection before severe immune deficiency has developed. Therefore, the cell-mediated arm of immune functions is lost earlier and to a greater extent than the humoral antibody arm. As the CD4+ cell counts drop, the helper functions of T cells decline resulting in reduced capacity of B lymphocytes (as plasma cells) to respond by antibody synthesis and secretion.

Most vaccines in current use are intended to induce antibody responses and it is therefore important to vaccinate HIV infected children earlier rather than later. CD4+ cell numbers and functions are near-normal even in infants who had been perinatally infected with HIV; therefore they would respond well to most vaccines. As CD4+ cells drop in number and functions, the ability to respond to new antigens declines. Eventually, even pre-existing pathogen-specific immunity will decline. But the chances of administration of antiretroviral therapy would be higher as children grow older; hence it is important

to vaccinate rather than to vacillate on account of the anxiety about the safety, efficacy and necessity to vaccinate. Once a child is on antiretroviral multidrug therapy, we assume that the immune functions are near-normal for the purpose of vaccinations.

Epidemiology

The pandemic of HIV infection was first detected in India in 1986.[1] Unlike the then popular belief that it transmitted mostly among men having sex with men, the evidence showed that the predominant mode of transmission in India was heterosexual sexual contact.[2] In general, the behavior of men and women in extra-marital sexual contacts was found to be rather unique in India, in that men by far were more "promiscuous" than women.[3] That was interpreted and translated into an unexpected transmission chain in which far fewer numbers of women (mainly sex workers) had sex with much larger numbers of men. This was one reason why HIV transmission did not spread as fast and as frequently in India as in many nations in other cultures with a more balanced equation of promiscuity between men and women. On the other hand, this created an unanticipated phenomenon in which monogamously married women without any recognized "risk behavior" would be vulnerable to HIV infection if husbands were promiscuous. That hypothesis was confirmed among pregnant women in Tamil Nadu.[4] Thus, mother-to-infant transmission of HIV had to be expected.

The Indian Council of Medical Research had established a Task Force on AIDS in 1986 soon after the detection of HIV infection in India.[5] The Task Force conducted regular periodic sentinel-based surveys for measuring the sequential annual prevalence of infection in 39 cities.[5] The study populations included women sex workers and men with sexually transmitted diseases (STDs) as "high-risk" groups for HIV infection and pregnant women as a "low-risk" group.[5] The latter population samples were continued for sentinel surveys under the National AIDS Control Organization when it took over the HIV/AIDS investigations and control activities from the Task Force, in 1992.[6] Thus, considerable amount of data had been collected on the potential problem of mother-to-child transmission of HIV infection from the very beginning of India's response to the pandemic spread of HIV.

Under natural conditions the perinatal transmission frequency of HIV infection is about 30 percent.[7] However, relatively simple interventions such as maternal screening for infection and antiretroviral prophylaxis for infected mothers without closely restricting breastfeeding brought down the frequency to 6.5 percent (95% CI 1.4-17.9%), in one center in Tamil Nadu.[8] In a study in Mumbai, the perinatal transmission could be reduced to <2 percent when zidovudine was given to mothers from 14 weeks of pregnancy and to infants for 6 weeks, along with avoidance of breastfeeding.[9]

Among young children with HIV infection in Mumbai, 84-87 percent were perinatally acquired and the rest were infected through blood transfusion.[10,11] By the time infection was diagnosed (at or after 18 months), 78 percent had already been vaccinated with several vaccine doses.[11] The reported mortality of perinatally infected children is 22 percent by 18 months.[12] All the above data show that under natural conditions, schedule-based vaccinations are likely to have begun or be completed by the age (18 months) a toddler may be diagnosed with HIV infection.

Recent Development in Vaccination of HIV Infected Infants

There has been a recent shift in the World Health Organization's (WHO) recommendation regarding BCG vaccination of infants with HIV infection.[13] Accordingly, the WHO recommends not giving BCG to children known to be infected with HIV—when the infection status in unknown, it is better to give BCG rather than delay it until the situation is clarified by appropriate laboratory tests.[13] The rationale is the experience in South Africa and Argentina that HIV infected children may develop disseminated BCG disease at the frequency of approximately 1 percent.[13]

The WHO has noted that the Danish and Pasteur strains of BCG are used in these two countries. Thailand and Brazil, two countries with reliable HIV and tuberculosis reporting systems have not reported such frequency of disseminated BCG disease—there the less reactogenic Moreau and Japanese strains are used. Therefore, the importance of strain in causing dissemination should be explored further.[13]

India's reporting of diseases within the health system is primitive, both in terms of quality and coverage; there is no public health disease surveillance system and laboratory support services are unavailable to the public sector primary and secondary healthcare institutions. Therefore, the situation is unclear in India although the Danish strain of BCG is utilized. There are anecdotal instances of what might be either disseminated BCG disease or early disseminated tuberculosis in BCG vaccinated children—the two can be distinguished only by careful microbiology. Thus, Indian data will be unlikely to help unless new data emerge through research.

Multidrug antiretroviral treatment protects children from disseminated BCG disease but may lead to immune reconstitution inflammatory syndrome in HIV infected BCG-vaccinated children.[13] However, between the two

risks, administering BCG to children under antiretroviral treatment offers less-risk and more benefit; hence children who had not been given BCG earlier should be preferably vaccinated after antiviral treatment has been started.

The WHO has also recently published a revised position paper on measles vaccination.[14] Accordingly, the measles vaccine should be routinely administered to potentially susceptible, asymptomatic HIV-positive children and adults.[14] In areas where there is a high incidence of both HIV infection and measles, the first dose of measles vaccine may be offered as early as 6 months. Two additional doses of measles vaccine should be administered to these children according to the National Immunization Schedule.[14] Even children with symptomatic HIV infection who are not severely immunosuppressed but are nonetheless susceptible to measles may be offered the measles vaccine as the risk of natural disease far outweighs the risk of vaccination. The safety of measles vaccine in HIV infected persons was recently analyzed by the Global Advisory Committee on Vaccine Safety and the above summary recommendations have emerged from the report of the committee.[15]

Recommendations Regarding Vaccines and Schedules

The Immunization Division of the Department of Family Welfare, Ministry of Health, Government of India is in charge of the Universal Immunization Program (UIP) in India. The division has not made any formal recommendations or guidelines regarding vaccinations in HIV infected children. Another feature of the UIP vaccination schedule is that only BCG, OPV, DPT and measles vaccines are included in infancy, followed by DPT boosters in the 2nd and 6th years of life. Unless an infant is severely/chronically ill all "routine" UIP vaccinations are both safe and necessary.

The Indian Academy of Pediatrics (IAP) has established guidelines for vaccinating children with HIV infection.[16] HIV infected children are categorized as either asymptomatic or symptomatic for this purpose. However, as mentioned above, under ordinary conditions the presence of HIV infection will be determined only by 18 months of age, at which point the primary doses of all relevant vaccines, including mid-second year booster(s) would already have been given as if the child was not HIV infected.

While the WHO recommends OPV for all children (including those with HIV infection), IAP recommends IPV for symptomatic and even asymptomatic HIV infected infants.[16] The IAP schedule is IPV at 6, 10 and 14 weeks (as per National Immunization Schedule (Table 5.2.1) age for OPV) followed by a booster at 15-18 months and at 5 years.[16] IPV is preferred over OPV for anyone with close contact with the HIV infected infant. If the family cannot afford IPV, the same schedule is recommended for OPV. The IAP guidelines seem to be silent on a dose of OPV soon after birth, while the WHO recommends the same.

Regarding the measles vaccine, IAP agrees with the WHO recommendations of giving a dose at 6 months and at 9 months. The National Immunisation Program does not offer another dose of the measles vaccine, but IAP guidelines include a dose of MMR vaccine (in the second year of life) provided CD4+ cell count is >15 percent.[16] IAP recommends the regular schedule of hepatitis B vaccination for all infants who are asymptomatic; for symptomatic infants and children a four dose-schedule using double-dose vaccine is recommended. Additionally antibody testing is also recommended, with "regular boosters" as demanded by antibody levels.[16] Regarding the hepatitis A vaccine (killed virus vaccine), a regular schedule followed by antibody monitoring and administration of booster(s) if necessary are recommended.[16] IAP also recommends *Hemophilus influenzae* B vaccine and pneumococcal conjugate vaccine, as in the case of all infants not infected with HIV.[16]

Specific Problems and Solutions

Once children have been diagnosed with HIV infection, plans for further vaccinations should be made on an individualized basis rather than by following schedules used in immunocompetent children. T cell activation influences the balance between latent infection and productive infection; activated cells tend to shift from latency to productive viral replication. Therefore unnecessary vaccinations should be avoided particularly when the risk of the target disease is low. For example, killed virus influenza vaccine given to children was shown to increase the numbers of activated T cells (CD25+) and also HIV viral load during a short interval of less than 6-8 weeks, which rebounded to pre-vaccination levels without in any way altering the clinical signs/symptoms related to HIV infection.[17] Similarly, a drop in CD4+ cell count following influenza vaccination has been shown in adults also.[18] However, where seasonal influenza is a health hazard, annual influenza vaccination is given to HIV infected adults, particularly when they are on antiviral therapy.

On the other hand, the varicella vaccine does not show such an adverse influence on HIV infection and is strongly recommended in order to prevent chickenpox which could become severe in HIV infected children.[19] However, the vaccine efficacy is less than in normal individuals. Thus, two doses of varicella vaccine results in seroconversion in 60 percent of vaccinated children, while 83 percent have evidence of cell-mediated immune

Table 5.2.1: List of immunizations for HIV exposed infected children

Vaccine	*Dose and route of administration*	*Schedule*	*Boosters*	*Adverse effects*	*Remarks*
BCG	0.1 ml Intradermal	At birth		Disseminated BCG disease, persistent ulcer, lymphadenopathy	Not to be given to symptomatic children
DPT	0.5 ml deep IM	6 weeks 10 weeks 14 weeks	18 months 5 years	Fever, pain, incessant crying, encephalopathy	Safe in symptomatic children
OPV	2 drops oral	6 weeks 10 weeks 14 weeks	18 months 5 years	Vaccine associated paralytic poliomyelitis	The WHO recommends the use of OPV in HIV infected children, but the United States Advisory Committee on Immunization prefers that it be avoided and IPV used instead
Hep B	0.5 ml IM	Birth 1-2 months 6-18 months	Should be considered if anti-HBs levels <10 mIU/ml	Induration, soreness at site	Double dosing for symptomatic children
Measles	0.5 ml Subcut	9 months	Can be given at 6 months in outbreak, followed by repeat dose at 15-18 months	Mild illness with fever, rash	Not recommended if CD4+ age specific percentage ≤15%
Hemophilus influenza type B (HIB)	0.5 ml IM	2 months 4 months 6 months 12-18 months		Local pain, tenderness	Safe in symptomatic children
Rotavirus	Oral	2 months 4 months 6 months		Hypersensitivity reactions	Safe in symptomatic children
Pneumococcal Conjugate Vaccine (PCV)	0.5 ml IM	2 months 4 months 6 months	12-15 months	Hypersensitivity reactions, low fever, pain	Children aged ≥2 years should also receive the 23-valent pneumococcal polysaccharide vaccine (PPV) more than 2 months following the last PCV dose, and should receive a single revaccination with the PPV 3-5 years later.
Varicella	0.5 ml Subcut	12 months 15 months		Hypersensitivity, local pain, low fever	Not recommended if CD4+ age specific percentage ≤15%
Trivalent Inactivated Influenza Vaccine (TIV)	0.25 ml IM if aged 6-35 months, 0.5 ml if aged >3 years	Yearly between 6 months and 6 years of age		Induration, local tenderness, fever, allergy to egg protein	Safe in symptomatic children (but not aged <6 years)

Contd...

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Hepatitis A	0.5 ml IM	2 doses, 6 months apart between 12 and 23 months of age		Induration, local tenderness	Safe in symptomatic children
MMR	0.5 ml SC	12 months 13 months		Lymphadenopathy, arthralgias, rash	Not recommended if CD4+ age specific percentage <15%, or for those with measles immunity
Meningococcal Conjugate Vaccine (MCV4)	0.5 ml IM/SC	2-6 years		Headache, irritability, Guillain-Barré Syndrome (GBS), local tenderness	Especially indicated in terminal complement deficiencies, asplenia; Contraindicated in patients with h/o hyper-sensitivity to components or h/o GBS; Revaccination with MCV4 recommended in children immunized with Meningococcal Polysaccharide Vaccine (MPSV4) >3 years previously
Human Papilloma Virus (HPV) Vaccine	0.5 ml IM	1st dose to females aged 11-12 years 2nd dose 2 months after 1st dose 3rd dose 6 months after 1st dose		Hypersensitivity reactions	Females only; Avoid in pregnancy
Typhoid ViCPS (Vi Capsule Polysaccharide)	0.5 ml SC/IM	Single dose for children > 2 years	Every 3 years	Local pain, swelling	Endemic areas
Injectable Polio Vaccine (IPV)	0.5 ml SC/IM	2 months 4 months 6-18 months	4-6 years	Local pain, redness, hypersensitivity	Safe in symptomatic children

Acknowledgements to Dr Mamatha M. Lala and Ms Noor Ahmed for compiling the table

response; 79 percent are protected from severe disease as they develop antibody or cell-mediated immunity.[19]

The reduced vaccine efficacy has been well illustrated with the hepatitis B vaccine. Since, hepatitis B infection in HIV infected persons is associated with an increased frequency of progression to chronic hepatitis B and a decreased frequency of HBe antigen clearance, it is important to vaccinate them with the hepatitis B vaccine. However, immune responses are less robust than in immunocompetent children. Two approaches have been proposed to overcome this inhibitory effect. One is to give a second course of the hepatitis B vaccine. In children who had already received three doses, an additional three doses improved antibody response.[20] The first course of vaccination, given as three doses one month apart, resulted in immune response frequencies which were determined by the CD4+ cell counts. Those with >500 cell counts had 88 percent response, while those with <500 cells had only 33 percent response.[20] After repeating the course once more, 7 of 9 nonresponders also responded.[20] Another option is to double the dose of the hepatitis B vaccine for improved vaccine efficacy.[21] When the vaccine was given in the 0-1-6-month-course, statistically significantly more individuals responded to the double dose regimen (47% versus 34%). Those with CD4+ cell counts of > 350 responded better (64%) than those with less cells (26%). Similarly, those with a viral load < 10,000 responded better (58%) than those with a higher load (16%).

In countries like India and Thailand where stray dogs are rampant, dog bites and rabies are frequent. While

HIV infected children may not have a higher-risk of animal bite compared to others, consideration may be given to pre-exposure prophylaxis using the modern cell-culture based rabies vaccines. It is encouraging that such a course did not reduce CD4+ cell count nor increase the HIV viral load.[22]

Regarding polio vaccination, the WHO continues to recommend OPV in spite of HIV infection, whereas, the United States Advisory Committee on Immunization recommends that it be not used. This precaution seems to be based on theoretical grounds without any observed adverse effects due to OPV.[23]

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5.3

Management of HIV Infection During Infancy

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For some time, children have not featured very strongly in the global response to the HIV pandemic. Advocacy campaigns conducted over the last 5-10 years, particularly the 'Unite for Children, Unite against AIDS' initiative launched by the United Nations Children's Emergency Fund (UNICEF) in October 2005 have helped to galvanize the global response to the pediatric pandemic, resulting in improved access to life-saving interventions for HIV infected children, including increased access to cotrimoxazole prophylaxis and antiretroviral therapy (ART).[1] Developments clarifying the case-management of pediatric HIV infection and related opportunistic infections have greatly assisted this process. However, the care needs of very young HIV infected children continue to be neglected. A fledgling body of research has shown that the first two years of life of an HIV infected child represents an extremely vulnerable phase, associated with high risk of rapid disease progression and/or death. Consequently, there is an urgency to confirm the HIV diagnosis during early infancy and address the specific care and treatment needs of this patient sub-group, to prevent undue health-related complications, limit HIV-related under-5 mortality and moderate the financial and health system impacts associated with hospitalization for severe opportunistic infections. This matter has become important for HIV child health professionals in resource-limited settings characterized by high population HIV prevalence and where HIV infection contributes substantially to under-5 mortality.

This chapter focuses on several aspects of HIV infection during infancy (i.e. in children less than 12 months old) including:

- Clinical manifestations of HIV infection
- Risk factors associated with disease progression
- Management of the asymptomatic young child
- Severe opportunistic infections in undiagnosed or newly diagnosed infants
- Benefits of early ART
- Relevant antiretroviral drug and regimen issues.

Clinical Manifestations

Does Primary HIV Infection Manifest in Young Children?

Early literature describing the natural history of perinatally-acquired pediatric HIV infection in resource-rich settings indicated that the disease has a bimodal-clinical expression. Up to 25 percent of infected children follow an accelerated clinical course characterized by severe symptomatic infections. These children have been called 'rapid progressors'. The majority experience a slowly progressive disease course and have been called 'slow progressors'.[2] By contrast, the natural course of horizontally acquired HIV infection in adolescents and adults usually progresses through a typical sequence of discrete phases, i.e. primary infection (8-12 weeks), clinical latency (7-10 years), symptomatic disease (1-2 years), and advanced symptomatic disease or AIDS (12-18 months) culminating in death.[3] In sub-Saharan Africa, pediatric HIV infection commonly causes rapidly progressive disease without evidence of these distinct clinical phases.

Primary or acute HIV infection in adults manifests with a collection of features, which may be recognized as a discrete clinical entity. The onset usually presents within days to weeks after HIV infection. Common features include fever, fatigue, rash, headache, tender lymphadenopathy, pharyngitis, myalgia and arthralgia. Night sweats, aseptic meningitis, oral ulcers, thrombocytopenia, leukopenia and elevated liver enzyme concentrations occur less frequently. The duration of the condition ranges from a few days to more than 10 weeks, but is typically less than 14 days.[4,5] Febrile illnesses are

common during infancy. Therefore, the recognition of acute HIV infection following perinatal transmission may be difficult because the clinical features overlap with those of common childhood infections. Despite this potential problem, characterization of the features of acute HIV infection in infancy was undertaken in a cohort study involving 56 Kenyan children. In those with early HIV infection (diagnosed before 2 months of age), the mean age during acute infection was 1 month, whereas in those with late postnatal HIV infection, the mean age during acute infection was 6.6 months. Forty-seven children (84%) developed at least 1 symptom during the acute infection window period. Acute HIV infection was statistically associated with skin rash, failure to thrive, and lymphadenopathy. In infants ≥ 2 months old, acute HIV infection was associated with pneumonia and dehydration. These results suggest that many HIV infected infants manifest with signs of acute HIV infection and that the presence of features strongly associated with acute infection may assist with the diagnosis of HIV infection during the first few months of life (Box 5.3.1).[6]

Box 5.3.1: Features strongly associated with acute HIV infection during infancy

- Skin rash, failure to thrive and generalized lymphadenopathy
- Additional features in infants ≥2 months old: pneumonia, dehydration.

Symptomatic Disease

The clinical features of pediatric HIV infection have been classified according to their prognostic significance by both the Centers for Diseases Control and Prevention (CDC) and the World Health Organization (WHO). The WHO classification is widely used in resource-limited settings.[7,8] Early features of pediatric HIV infection are usually a combination of generalized lymphadenopathy, hepatomegaly and splenomegaly. Clinical manifestations indicative of symptomatic disease develop quite rapidly i.e. 64 percent of HIV infected infants have some feature of HIV infection by 3 months, 83 percent by 6 months and 90 percent by 12 months of age.[9] Life table analysis subsequently showed that 23 percent progress to advanced infection or AIDS by 12 months of age.[10] HIV encephalopathy, a feature of advanced infection or AIDS, is associated with a high risk of developing long-term or permanent neurological and / or neurocognitive sequelae. Cohort studies have shown that approximately 10 percent of HIV infected children develop HIV encephalopathy during the first 12 months of life.[11,12] HIV encephalopathy represents the first AIDS-defining condition in more than 60 percent of children and the only AIDS-defining condition in 25 percent of young children.[12]

Research from resource-limited countries has partly evaluated the development of symptomatic disease during infancy. In one Ugandan study of 206 HIV infected children, 87 percent of all those less than 2 years of age had symptomatic disease at the time of assessment.[13] A prospective natural history study completed in Rwanda (n = 54) confirmed that failure to thrive and persistent generalized lymphadenopathy were common presenting clinical signs of pediatric HIV infection. During a 27 months follow-up period all 54 children presented with at least one HIV-related clinical feature, i.e. 34 (63%) presented with one symptom or sign, 11 (20%) with two and 9 (17%) with more than two features. Although, the frequency of symptomatic disease during the first year was not stated, the cumulative probability of developing AIDS by 12 months of age was 17 percent.[14] A Malawian cohort study of 190 HIV infected children, showed that the disease advanced rapidly resulting in 89 percent mortality after 3 years. However, during the first 12 months of life, 50 percent remained asymptomatic, 40 percent developed CDC category B symptomatic disease and 10 percent died.[15]

In a South African cohort study (n = 48), 70 percent and 77 percent of infected children had symptomatic disease by 6 and 12 months of age respectively, and AIDS was present in 44 percent by 12 months of age.[16] Disease progression was estimated recently in South African infants enrolled in the Children with HIV Early Antiretroviral Therapy (CHER) trial. By 12 months of age approximately 40 percent of infants had progressed to advanced infection (CDC clinical category C or advanced clinical category B disease) or death.[17] Neurocognitive deficits have been documented in African infants.[18,19] In one Rwandan cohort study, 16 percent of children had evidence of neurocognitive dysfunction by 12 months of age.[19] Few Indian studies have addressed the evolution of HIV-related features in infected children.[20,21] There are no published prospective cohort studies on this subject.[22] Hence the frequency of symptomatic disease including advanced infection or AIDS in infants in India remains unclear. It is generally accepted that disease progression is much faster in resource-limited than Western settings.[23] This brief literature review has shown that during infancy the prevalence of any symptomatic disease is generally high, but progression to advanced infection or AIDS is usually greater in African than European children (Box 5.3.2).

Box 5.3.2: Symptomatic HIV infection

- The majority of perinatally HIV infected children develop clinical features of the disease during the first year of life
- In general, a higher proportion of infants in resource-limited settings than in Western countries will progress to advanced HIV infection or AIDS during the first year of life.

HIV-related Mortality

In the European multicenter natural history study, the mortality rate in HIV infected children during the first 12 months of life was 17 percent.[9] In contrast, a large pooled analysis investigating mortality in HIV infected children in Africa showed that 35.2 percent died by 1 year of age and 52.5 percent by the age of 2 years.[24] A striking peak in HIV-related deaths was documented at 2-3 months of age in a South African study analysing pediatric mortality, thus highlighting the vulnerability of HIV infected infants during the first 6 months of life.[25] Indian studies have reported high mortality during the first year of life.[22] In one prospective study from Manipur (India), of 22 HIV infected neonates, 10 died within 8 weeks of birth and the remaining 12 died by 15 months of age (Box 5.3.3).[26]

Risk Factors for Disease Progression and Death during Infancy

A large meta-analysis, the HIV pediatric prognostic collaborative study (HPPCS) explored estimates of short-term disease progression using age, CD4 percentage, CD4 count and viral load in HIV infected children based in resource-rich settings on no ART or zidovudine monotherapy. In infants, short-term progression (during the ensuing 12 months) to AIDS or death was always greater than 10 percent irrespective of whether the CD4 percentage was normal or reduced. Thus infancy *per se* was identified as a strong risk factor for disease progression and death. Reliable CD4 count and percentage cut-off values of disease progression were not identified.[27,28] A similar study which combined longitudinal data on ART-naïve children from 10 studies in resource-limited settings, the Cross Continents Collaboration for Kids (3Cs4Kids), showed that at any CD4 count or percentage children in resource-limited settings were at higher risk for disease progression than those enrolled on the HPPCS. Unfortunately children less than 12 months of age were not included in the 3Cs4Kids analysis. Therefore, these observations cannot be directly extrapolated to infected infants.[29]

Box 5.3.3: HIV-associated mortality

- During infancy, HIV-associated mortality is greater in resource-limited settings than in rich countries
- Without effective therapy at least 35 percent of HIV infected infants will die during the first year of life in poor countries
- There are no reliable predictors of disease progression and death during the first year of life in HIV infected infants. Because of the high risk of disease progression, all infected infants should be treated with ART, irrespective of their clinical condition or CD4 count.

The high rate of disease progression among HIV infected infants caused many treatment centers in the United States and Europe to initiate ART in all infants, following the introduction of triple combination antiretroviral therapy to pediatric practice in the mid-1990s.[30] The CHER study, a randomized trial of early versus late initiation of ART recently showed a 76 percent reduction in mortality and a 75 percent reduced risk of disease progression in infants initiating ART before the age of 3 months.[17] Following the release of these results, the WHO, European, and American guidelines committees recommended that all infants less than 12 months of age should be started on ART soon after diagnosis, irrespective of their clinical severity or immunological stage.[31,32]

Confirming HIV Infection

Tests that detect pro-viral DNA (HIV DNA PCR), viral RNA (Viral load) or viral protein (Ultrasensitive p24 assays) are used to confirm HIV infection during infancy. Access to these sophisticated assays is increasing in poor countries, aided by dried blood spot methodology for collecting patient blood samples. However, many areas in poor countries are still unable to use these tests routinely for a variety of reasons including limited availability (e.g. for research purposes only), inadequate laboratory infrastructure, suboptimal laboratory quality control systems, and shortages of trained laboratory technologists.[33] In these settings the WHO has recommended that a presumptive diagnosis of HIV infection should be made, based on a positive HIV antibody test and the presence of specific clinical features (Table 5.3.1).[8]

The performance of the WHO presumptive diagnostic criteria against HIV DNA PCR testing was evaluated in 3 recently conducted studies (Table 5.3.2).[34-36] The WHO presumptive diagnostic criteria were more sensitive than the integrated management of childhood illnesses (IMCI) criteria for identifying suspected HIV infection without compromising specificity.[34] The results of the study undertaken by the African Network for the Care of Children with HIV/AIDS (ANECCA) indicated that the WHO presumptive diagnostic criteria had an accuracy of 74.5 percent for identifying children in need of ART (Table 5.3.2).[36] Therefore, in settings where viral testing is not possible the WHO presumptive diagnostic criteria should be used to diagnose HIV infection in young children and to start appropriate interventions including ART. In settings where viral testing is possible but where there are delays of ≥ 2 weeks in reporting or obtaining the results, strongly consider initiating ART in children who fulfil the criteria for presumptive HIV diagnosis before the viral test result is known (Table 5.3.1). Once the result of viral testing are made available treatment decisions may be revised, if

Table 5.3.1: Diagnostic criteria for presumptive diagnosis of severe HIV infection in children <18 months old[8]

1. The child is confirmed to be HIV antibody positive
AND

2a. The infant is symptomatic with two or more of the following:
- Oral thrush
- Severe pneumonia
- Severe sepsis

OR

2b. Diagnosis of any AIDS-indicator condition(s) such as pneumocystis pneumonia, cryptococcal meningitis, severe wasting, severe malnutrition, Kaposi's sarcoma, or extrapulmonary TB

3. Other supportive evidence of severe HIV disease in an HIV-seropositive infant:
- Recent HIV-related maternal death or advanced HIV disease
- Child's CD4 percent <20 percent

The diagnosis of HIV infection should be confirmed as soon as possible

Table 5.3.2: Performance of the WHO presumptive criteria against HIV DNA PCR testing for diagnosing HIV infection in HIV-antibody positive children <18 months of age

Study	*Criteria*	*Number*	*Sensitivity (%)*	*Specificity (%)*	*PPV[d] (%)*	*NPV[e] (%)*
Inwani et al[33]	WHO-PD criteria[a]	80 HIV DNA PCR positive 54 HIV DNA PCR negative	43	88	54	82
Inwani et al[33]	WHO-PD plus CD4%[b]	80 HIV DNA PCR positive 54 HIV DNA PCR negative	84	41	32	88
Peltier et al[34]	WHO-PD criteria[a]	124 HIV DNA PCR positive 112 HIV DNA PCR negative	76.6	52.7	64.1	67
Peltier et al[34]	WHO-PD plus low CD4[c]	124 HIV DNA PCR positive 112 HIV DNA PCR negative	88.7	42.9	63.2	77.4
ANECCA[35]	WHO-PD criteria[a]	141 HIV DNA PCR positive 160 HIV DNA PCR negative	68.9	81.0	71.2	79.2

[a]WHO presumptive diagnostic criteria[8]
[b]WHO presumptive clinical diagnostic criteria[8] plus low CD4 percent [CD4%<25% if <12 months, or <20% if 12-18 months old]
[c]WHO presumptive clinical diagnostic criteria plus low CD4 [CD4<1500 cells/mm^3 or < 25 percent if <12 months, or CD4 <750 cells/mm^3 or <20 percent if 12-18 months old]
[d]Positive predictive value
[e]Negative predictive value

necessary. This approach may prevent undue delay in starting ART, which often results in disease progression and/or death during infancy.[17]

Prophylaxis and Treatment

Cotrimoxazole Prophylaxis

A randomized placebo-controlled trail conducted in Zambia showed that cotrimoxazole prophylaxis reduced mortality and hospitalization rates by 43 percent and 23 percent respectively over a 19-month period, in HIV infected children aged 1-14 years.[37] In keeping with existing global policy, primary cotrimoxazole prophylaxis is recommended for all HIV-exposed and infected children from the age of 4-6 weeks. In infants in whom HIV infection is excluded, prophylaxis should be discontinued. However, for infected infants cotrimoxazole should be continued beyond the first year of life.[38]

Isoniazid Prophylaxis

Every HIV infected child irrespective of age, with a household tuberculosis (TB) contact should be screened for active TB. If there is no evidence of active TB, the child should be provided with post-exposure isoniazid (INH) prophylaxis, i.e. INH 10-20 mg/kg/day for 6 months.[39] Two placebo-controlled clinical trials that addressed whether INH prophylaxis should be routinely administered to HIV infected children, have yielded conflicting results. Both trials were stopped early by the respective data safety monitoring boards. The first study involved 263 children (median age: 24.7 months) followed for 5.7 months, 9 percent of whom were on ART. Incident TB and all cause of mortality were significantly reduced in the INH prophylaxis group by 72 percent and 44 percent respectively.[40] The second study, a phase II/III trial randomized 452 infants to receive INH 10-20 mg/kg/day or placebo. None of the infants had been previously exposed to TB. After a median follow-up period of 36 weeks, 39 (17.3%) and 32 (14.2%) children in the INH and placebo groups respectively, developed TB or had died. This difference was not statistically significant ($p = 0.34$) implying that INH prophylaxis did not improve TB disease-free survival. At the time that this trial was stopped 66 percent of the participants had commenced ART.[41] Consequently, WHO has recently recommended that HIV infected children less than 12 months of age should

receive post-exposure INH prophylaxis but not routine, preexposure isoniazid preventive therapy (IPT).

ART for Asymptomatic Infants

Given the high risk of disease progression and death, and the lack of reliable risk factors predicting disease progression during the first year of life, the WHO recommended in April 2008 that all children less than 12 months of age with confirmed HIV infection should commence ART as soon as possible, irrespective of their clinical severity or immunological status. Anecdotal observation from our personal clinical practice together with published observational information suggests the first 6 months is an extremely vulnerable period and consequently ART during early infancy should be regarded as a relative medical emergency.[25] However, the reality in many resource-limited settings is that HIV infected infants are not being adequately prioritised for ART.

A systematic review on the effectiveness of ART in sub-Saharan Africa published in 2008 showed that in only 2 of 30 treatment programs, was the median age at commencement of ART less than 2 years.[42] A more recent analysis that included more than 6000 children, representing 20 percent of all children enrolled on ART in the South African national pediatric ART program showed that the situation is gradually improving. In that study, 28.9 percent of children starting ART were less than 18 months old, an improvement on the results of the systematic review.[43] As treatment programs implement the WHO recommendation for HIV infected infants, an increasing proportion of children enrolled on ART should be less than 12 months of age (Box 5.3.4). Therefore, median age at enrolment may be regarded as an important qualitative measure of how well pediatric ART programs are responding to the care and treatment needs of young children with HIV infection. Effective response to this patient subgroup is of particular relevance to countries with high pediatric HIV prevalence because of the potential positive impact on under-5 mortality. Failure to improve prevention of mother-to-child transmission (PMTCT) intervention coverage and provide effective care for young HIV infected children will undermine efforts to achieve Millennium Development Goal number 4 (MDG 4) in countries with a high burden of HIV; MGD 4 aims to reduce under-5 mortality by two-thirds by 2015 compared to under-5 mortality in 1990.

Box 5.3.4: ART during infancy

- ART should be started immediately after pre-ART initiation counselling has been satisfactorily completed, ideally within 2 weeks of confirming the diagnosis of HIV infection.

Severe Opportunistic Infection

Despite concerted efforts to improve the effectiveness and coverage of PMTCT interventions in resource-limited settings, many HIV infected children still present for the first time to the health system with unknown HIV status and opportunistic infections. Frequently, undiagnosed infants manifest with common childhood infections such as pneumonia, sepsis or gastroenteritis, requiring hospitalization and in-patient care. There are several reasons why this situation persists in poor countries including (1) inadequate PMTCT intervention coverage resulting in high vertical transmission rates, (2) PMTCT intervention failures because prophylactic measures are never 100 percent effective, (3) high lost-to-follow-up rates from PMTCT intervention programs and during the process of referring HIV infected infants to ART programs resulting in sub-optimal care during the asymptomatic stage of pediatric HIV infection, and (4) delays in responding to the care needs of HIV infected infants because of health system deficiencies such as failure to appreciate the vulnerability of young infected children, high patient volumes, staff shortages and the competing interests of adult patients.

Our institution, a tertiary referral hospital is located in a province with high HIV prevalence and a functional PMTCT intervention program. Currently, between 50 percent and 60 percent of children enrolled on ART at our hospital are less than 6 months of age. They usually present with severe opportunistic infection and undiagnosed or recently diagnosed HIV infection.[44] During the first few days of hospitalization, the diagnosis of HIV infection is usually confirmed on DNA PCR testing. The most common reason for admission is acute severe pneumonia. A survey in 2007 showed that acute severe pneumonia with or without associated sepsis was responsible for 61.8 percent of HIV-related deaths in the general pediatric wards of our hospital.[45]

HIV-associated pneumonia may be caused by a wide spectrum of microorganisms (Table 5.3.3). Polymicrobial pneumonia, i.e. infection caused by two or more microbes, is extremely common in both HIV infected

Table 5.3.3: Microbes associated with acute severe pneumonia

- **Bacteria:** *S. pneumoniae, S. aureus, H. influenzae, E. coli, K. pneumoniae, Psuedomonas* sp. *Salmonella* sp
- **Viruses:** RSV, *Influenza, Parainfluenza, Adenovirus, Rhinovirus, metapneumovirus, Cytomegalovirus*
- **Fungi:** *Pneumocystis jirovecii, Candida* sp. *Apergillus* sp. *Cryptococcus* sp, other mycoses
- **Mycobacteria:** *M. tuberculosis, M. avium intracellulare*

and uninfected children in South Africa, and is associated with poor outcome.[46] At our hospital, infants with acute severe pneumonia (requiring in excess of 40 percent supplemental oxygen) are routinely screened by multiplex polymerase chain reaction (PCR) assay and immunofluorescence on nasopharyngeal aspirates for common respiratory viruses and *Pneumocystis jirovecii* respectively. In addition, gastric washings are obtained for microscopic visualization of acid-fast bacilli and mycobacterial culture, and a blood sample for cytomegalovirus (CMV) viral load. Less frequently, respiratory secretions are obtained by bronchoalveolar lavage in intubated infants, for viral studies and bacterial and fungal culture. Our anecdotal experience suggests that polymicrobial infections caused by varying combinations of copathogens (Table 5.3.3) are common in HIV infected infants presenting with acute severe pneumonia, and that CMV is a frequent copathogen. CMV infection is an important outcome determinant in pediatric HIV infection. A recent Kenyan study showed that the presence of CMV DNA in the plasma of pregnant HIV infected women near delivery was associated with a 4-fold increased mortality risk in their HIV infected children during the first two years of life.[47] Most HIV infected and HIV-exposed, uninfected infants acquire primary CMV infection postnatally at between 1 and 3 months of age.[48] An important implication of these observations is that broad-spectrum empiric antimicrobial therapy in HIV infected infants with severe pneumonia should ideally be directed against common viruses and bacteria, including CMV.

A standardized approach for managing acute severe pneumonia in HIV infected infants, developed at our hospital over the past 3 years is summarized in Table 5.3.4. Briefly, the HIV status of all hospitalised children is established usually within the first 3-5 days of admission, infants with severe pneumonia are screened for respiratory pathogens, broad-spectrum antibacterial, anti-*pneumocystis*, and anti-CMV therapy are initiated, and appropriate respiratory support provided. During the influenza season, oseltamivir is added to the empiric antimicrobial regimen. Once the results of the laboratory investigations are available, antimicrobial revision and/or rationalization may be required. For example, if the screen for CMV infection was negative, gancyclovir is discontinued, or if an unanticipated resistant bacterium is obtained on blood culture, therapy is revised according to the antibiotic sensitivity pattern of the causative microorganism.

In HIV infected infants with opportunistic infections, ART is generally started as soon as the HIV diagnosis is confirmed, the parents/caregivers have been informed of the HIV status and the decision to treat their child with ART, blood samples were taken for baseline ART investigations, and the baseline liver function tests are normal or tending towards normality. Early introduction of ART may occasionally be delayed for medical reasons such as in the presence of markedly elevated liver function tests or if oral intake has been suspended for a gastrointestinal problem. In our experience, few children with severe opportunistic infections have developed severe immune reconstitution inflammatory syndrome

Table 5.3.4: Approach to acute severe pneumonia in HIV infected infants

If indicted, confirm HIV status using a viral test, e.g. HIV DNA PCR

Special investigations that may support diagnosis and define etiology:

- Chest radiograph
- Complete blood count and differential count
- Blood culture
- Nasopharyngeal aspirate to screen for *Pneumocystis jirovecii* and respiratory viruses
- Gastric washings or sputum for Acid-fast bacilli and mycobacterial culture
- Blood CMV viral load
- Bronchoalveolar lavage for viruses, bacteria and fungi

Empiric therapy to cover common viruses, bacteria and *Pneumocystis jirovecii*:

- [a]Ampicillin 50 mg/kg/dose 6-hourly and Gentamicin 7.5 mg/kg/dose once daily, for 7-10 days
- Cotrimoxazole 10 mg/kg (Trimethoprim component) IV loading dose followed by 5 mg/kg/dose IV / oral 6-hourly for 21 days
- Prednisone 2 mg/kg/day for 7-10 days then tail off over 7 days
- [c]Gancyclovir 5 mg/kg/dose 12-hourly for 14-21 days followed by valgancyclovir 15 mg/kg/dose 12-hourly for a further 3-4 weeks (total gancyclovir/valgancyclovir exposure = 6 weeks)
- [b,c]Oseltamavir for 5 days
  - <3 months old: 12 mg twice daily
  - 3-5 months old: 20 mg twice daily
  - 6-11 months old: 25 mg twice daily

Appropriate respiratory support from the following options:

- Nasal prong oxygen
- Supplemental oxygen via a head box
- Continuous positive airways pressure (CPAP) ventilation if >50% oxygen via a head box is required to maintain saturation of 90-95%
- Intermittent positive pressure ventilation (IPPV) if CPAP unable to provide adequate support
- High frequency oscillatory ventilation if IPPV unsuccessful

Optimize fluid and electrolyte balance and nutritional intake

Initiate antiretroviral therapy soon after HIV diagnosis is confirmed after informing caregiver; caregiver counseling may be completed during initial period on ART

Antimicrobial revisions and/or rationalization depending on the results of laboratory investigations

Notes:

[a] For suspected nosocomial infection, replace ampicillin and gentamicin with an appropriate second line antibiotic regimen, e.g. piperacillin/tazobactum and amikacin

[b] Only administered empirically during influenza season

[c] Gancyclovir and/or oseltamivir may be stopped if laboratory tests exclude CMV infection and/or influenza

(IRIS) events after the early initiation of ART. Aggressive management of severe opportunistic infections together with early ART has resulted in a decline of HIV-associated mortality by more than 60 percent at our institution over the last 5 years.

Benefits of Early Art

Disease progression may be rapid, particularly in infants who acquire HIV infection during the intrauterine period. Rapid immunological progression was documented in a cohort of 75 HIV infected infants, including 50 (68%) who acquired HIV infection during intrauterine life. By the age of 6 months, 85 percent of the cohort had progressed to a CD4 less than 20 percent.[49] Early introduction of ART is associated with several advantages including immunological preservation, immunological reconstitution, prevention of early-onset severe opportunistic infections and attenuated mortality.[17, 50-52] Prevalence of HIV encephalopathy is appreciably reduced.[51,53] Widespread access to ART results in reduced HIV-associated hospitalization.[54-56] Concern about suboptimal virological suppression may be unfounded as recent studies indicate that high suppression rates are achievable in HIV infected infants treated with early ART.[52,57,58] HIV infected infants are at a substantial risk for developing TB. A recent South African study documented a 24-fold higher risk for developing any type of TB and a 17-fold increased risk for disseminated TB in HIV infected infants compared to HIV-uninfected infants.[59] Studies in children have demonstrated that ART improves the immunological response to mycobacterial infection and reduces the risk of developing TB by 50-70 percent.[60-62] However, the impact on TB risk in infants treated with early ART remains unknown. An additional benefit of early ART identified in the CHER study is a statistically significant reduced risk for BCG-associated immune reconstitution inflammatory syndrome.[63] Despite these benefits, the long-term consequences of early ART remain to be elucidated.

Antiretroviral Considerations

Perinatal Nevirapine Exposure

A combination of two nucleoside reverse transcriptase inhibitors (NRTIs) and either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) is the recommended first-line regimen for patients requiring ART, irrespective of their age. Pediatric practice in resource-limited settings has tended to favor NNRTI-containing first line regimens. Recent studies have explored the effectiveness of NNRTI- and PI-containing ART regimens following perinatal nevirapine (NVP) exposure. The estimated prevalence of NVP resistance in infants after single-dose NVP exposure was 52.6 percent, and 16.5 percent after using single-dose NVP in combination with other antiretroviral agents.[64] Response to NVP-containing ART was initially evaluated in a small study of 25 infants, 13 of whom had been exposed to perinatal NVP and 12 who were not exposed. Six months after ART was initiated, 1 infant in the control group (8.3%) and 10 previously exposed to NVP (76.9%) had experienced virological failure. This difference was highly statistically significant suggesting that in this setting PI-containing regimens may be superior. However, this was not a randomized study, the sample size was small and the study design did not include a comparison of the efficacy of NVP-exposed HIV infected infants treated with either NNRTI- or PI-containing regimes.[65]

More recently, a phase II randomized control trial, the IMPAACT P1060 study provided strong evidence that PI-containing regimens are preferable in infants previously exposed to perinatal NVP. In this study, 286 children aged 6-35 months in 6 African countries were enrolled, 153 who had been exposed to single-dose NVP and 133 who had not received single-dose NVP. These children were randomized to receive NVP-containing ART or lopinavir/ritonavir (LPV/r)-containing ART. After 24 weeks of ART, 24 percent of the infants previously exposed to single-dose NVP and treated with a NVP-containing regimen failed to suppress HIV, compared to 7 percent of infants previously exposed to single-dose NVP but treated with a LPV/r-containing regimen. This difference was significant, $p = 0.027$, prompting the data safety monitoring board to recommend that the investigators stop enrolling HIV-exposed children on the study and that the treatment of children already on the study be reviewed to and if necessary re-optimised.[66] Therefore, routine PI-based first line therapy in HIV infected infants previously exposed to perinatal NVP is strongly recommended (Box 5.3.5).

A different strategy for managing HIV infected infants who were previously exposed to perinatal NVP, was explored in the NEVEREST trial. Briefly, 322 HIV infected infants previously exposed to perinatal NVP who met clinical and/or immunological criteria for ART were started on LPV/r-based ART. Those who achieved and maintained a viral load of <400 copies/ml for ≥3 months (n = 195)

Box 5.3.5: ART after nevirapine exposure

- Ideally infants commenced on ART after NVP exposure should receive a LPV/r-based regimen
- Once NVP-exposed HIV infected infants have achieved virological suppression on a LPV/r-containing regimen it may be possible to successfully switch them to a NVP-containing regimen. However, the conditions under which this may be done needs further clarity.

were randomized to either remain on the same regimen (n = 99) or substitute NVP for LPV/r (n = 95). The median age of the children was 11 months at ART initiation and 20 months at randomization. In an intention-to-treat analysis 24 weeks after randomization, 65.6 percent of children who were switched to NVP and 49.5 percent of children who remained on LPV/r were virologically suppressed (viral load <50 copies/ml), $p = 0.02$. However, fewer children in the NVP group maintained a viral load consistently <1000 copies/ml (84.9% vs 96.8%, $p = 0.007$). These findings suggest that under certain circumstances, children who were exposed to perinatal NVP may be switched from a LPV/r- to a NVP-containing ART regimen and so preserve LPV/r for the second line regimen.[67] Further research is required to better define the circumstances under which this therapeutic switch may be successfully achieved.

Lopinavir/Ritonavir Dosing

Lopinavir/ritonavir, available as a coformulated oral solution, is the most commonly used PI in infants and young children with HIV infection. A major advantage of LPV/r is its high 'resistance barrier', allowing the drug to remain active despite the accumulation of several protease resistance mutations in the viral population. Disadvantages of the oral solution include the offensive taste, high alcohol content (43%), and limited stability at room temperature. Pharmacokinetic evaluation in children 6 weeks to 6 months of age has shown that the clearance of LPV/r is higher than in older children, but a dose of LPV/r of 300 mg/75 mg/m^2 twice daily is sufficient to maintain the trough LPV concentration above 1 mg/ml in this age group.[68] The optimal dose in children less than 6 weeks old was explored in a pharmacokinetic study of 10 children. At a LPV/r dose of 300 mg/75 mg/m^2 twice daily the area under the curve (AUC) was significantly lower than in infants aged 6 weeks to 6 months. Virological control was achieved in 8 of the10 infants 24 weeks after starting ART. These findings suggest that while the starting dose of 300 mg/75 mg/m^2 twice daily is acceptable in these young infants, therapeutic drug monitoring should ideally be used to optimize dosing.[69] To further improve the administration of LPV/r in young children heat-stable, crushable or sprinkle formulations are urgently required.

Tuberculosis Co-treatment

When HIV-TB coinfection is present, rifampicin-containing antituberculous drug regimens induce the metabolism of lopinavir (LPV) by the cytochrome P450 hepatic enzyme system decreasing its serum concentration by more than 75 percent. In contrast, the protease inhibitor ritonavir is a potent inhibitor of the CYP 3A4 enzyme isoform. Therefore, by augmenting LPV/r-containing regimens with additional ritonavir, the effect of rifampicin on LPV concentration may be overcome in children cotreated with antituberculous medication. A pharmacokinetic study in HIV infected children with TB has indeed shown that by providing additional ritonavir to children receiving LPV/r to give a lopinavir: ritonavir ratio of 1 : 1, the effect of rifampicin on LPV metabolism may be attenuated. A minimum LPV concentration of >1 mg/ml was maintained in 13 of 15 children using this strategy, suggesting that ritonavir boosting is an important option for children receiving LPV/r and concomitant rifampicin. This study included children aged 7 months to 3.9 years. Whether this treatment option is effective in infants less than 6 months old is currently not known.[70] Furthermore, ritonavir is not widely available in resource-scarce settings and currently a heat-stable preparation does not exist. Consequently, alternative ART options notably triple NRTI therapy or NVP-containing regimens using a NVP dose at the upper end of the dosing range (i.e. 200 mg/m^2 per dose, twice daily) are used in children co-treated with rifampicin, despite limited information of the effectiveness of these strategies in HIV infected infants.[8,71,72]

Second Line Therapy after LPV/r

HIV infected children who fail perinatal NVP prophylaxis and are subsequently commenced on first line regimens containing LPV/r are extremely challenging to manage when they ultimately fail first line therapy. In future, effective second line options may include darunavir or raltegravir combined ideally with an optimized background regimen (OBR) consisting of at least two of any pediatric-approved NRTIs, NNRTIs (including etravirine) or entry inhibitors to which the viral population is responsive.

Darunavir, a second generation PI was recently licensed for use in children from the age of 6 years. It has been shown to exert activity against HIV isolates resistant to currently used PIs in both HIV infected adults and children.[73-75] Darunavir should ideally be administered with low-dose ritonavir. The Federal Drug Administration recently approved a 75 mg darunavir tablet for children aged 6 years or older. However, a coformulated product does not exist. Optimal dosing in children <6 years old has not yet been established but is under investigation. The bioavailability of darunavir following the administration of an oral solution to adult volunteers was shown to be comparable to that of the 300 mg tablet.[76] Further study is required to determine the relative efficacy of darunavir in children who fail LPV/r-containing first line therapy.

Raltegravir, an integrase inhibitor, has been approved for adult practice. The drug is currently not licensed for pediatric practice, although studies in children are underway to optimize dosing, and evaluate safety and effectiveness of raltegravir in treatment-experienced children and adolescents.[77] Recent results from a phase I/II trial of antiretroviral-experienced but integrase-naïve children aged 6-11 years with body weight ≥ 25 kg showed that raltegravir dosed at 400 mg twice daily in association with an OBR was well tolerated and 56 percent of the children achieved virological success at week 24.[78] Suitable formulations for young children are under development.[79] Evaluation of chewable and granule formulations in adult volunteers recently showed moderately better bioavailability when compared to licenced adult tablets, and comparable safety profiles.[80] Coadministration of rifampicin causes a 40-60 percent decrease in raltegravir concentration, complicating concomitant treatment of TB.[81] This could be problematic should raltegravir become accessible to HIV infected children in resource-constrained settings.

In many resource-limited settings these newer agents are not accessible. Potential therapeutic strategies after children fail a LPV/r-containing first line regimen include continuation of the failing LPV/r-containing regimen, switching to an NNRTI-containing regimen, switching to a holding regimen of lamivudine monotherapy until clinical or immunological deterioration occurs or new drugs become available or discontinuation of ART. Many clinicians in this situation persist with the existing LPV/r regimen once virological failure has occurred because the regimen may still be capable of suppressing the replication of wild-type virus while at the same time allowing the replication of biologically less-fit resistant mutants to continue. These mutants may cause less immunological damage. Hence administration of the failing regimen should slow down the rate of progression to immunological and ultimately clinical failure.

Conclusion

Recent pediatric HIV developments have focussed attention on the plight of young children. The extreme vulnerability of HIV infected infants as defined in natural history studies and the dramatic impact of ART and other interventions in attenuating the risk of disease progression and death in these children are indisputable observations. Consequently, treatment guidelines have been adapted to respond to this patient subgroup. Implementation of consensus treatment guidelines for HIV infected infants remains suboptimal in many resource-scarce settings. Overcoming delays in initiating effective therapy is perhaps the biggest challenge to transforming the outlook for these infants. Thus a renewed urgency is required to improve our collective response.

Further research is needed to advance the management of HIV infected infants. Questions that remain unanswered include (1) the safety and efficacy of cotrimoxazole prophylaxis in infants less than 6 weeks of age, and whether intervening with cotrimoxazole at birth in HIV-exposed infants may further lower their risk for *Pneumocytis jirovecii* and bacterial infections, (2) optimal ART strategies for infants co-treated with rifampicin-containing antituberculous drug regimens, (3) pharmacokinetics, dosing, safety and efficacy of raltegravir and the newer integrase inhibitors in HIV infected infants and young children, (4) optimal first and second line regimens for HIV infected infants and children previously exposed to perinatal nevirapine, (5) optimal childhood immunization strategies for HIV infected infants initiated on ART during early infancy, and (6) the long-term consequences and sustainability of ART initiated during early infancy.

Case Studies

Case 1

An infant aged 14 weeks is taken to the local clinic by his mother for routine immunization. The attending nurse discovers that mother and child have recently arrived from a rural area and did not participate in the local PMTCT intervention program. The mother consents to an HIV test. The infant's HIV rapid test is positive. The infant is completely asymptomatic.

1. **How should the child be managed?**
   The mother should receive post-test counseling.
   A viral test, e.g. HIV DNA PCR should be done to confirm the child's status.
   The child should be commenced on cotrimoxazole prophylaxis.
2. **A HIV DNA PCR test is requested. The mother returns a week later and learns that the result is positive. How should the child be managed?**
   The infant should remain on cotrimoxazole prophylaxis and be referred to the nearest ART center to start ART as soon as possible after pre-ART initiation counseling has been completed. In HIV infected infants ART should ideally be commenced within 2 weeks of confirming the diagnosis to prevent disease progression.
3. **What is the short-term risk of disease progression in HIV infected infants?**
   In HIV infected infants the risk of progression to AIDS or death is always greater than 10 percent irrespective of whether the CD4 percentage is normal or reduced.
4. **What ART regimen should ideally be administered to this infant?**
   The first line regimen should consist of two nucleoside reverse transcriptase inhibitors and either a protease

inhibitor or a non-nucleoside reverse transcriptase inhibitor (NNRTI). Because the infant was not exposed to antiretroviral agents during the perinatal period, nevirapine, a NNRTI may be used as the third drug.

5. **Should routine pre-exposure INH prophylaxis be prescribed?**
   Because of its uncertain efficacy, routine pre-exposure INH prophylaxis is not recommended in HIV infected children less than 12 months of age.
6. **What are the main benefits of early ART?**
   The benefits of early ART include immunological preservation, immunological reconstitution, prevention of early-onset severe opportunistic infections and a significant lower mortality risk.

CASE 2

A 4-month-old female infant presents with fever, cough and respiratory distress. Severe pneumonia is diagnosed. The attending doctor notes that the child has extensive oral thrush. An HIV rapid test is positive. An HIV DNA PCR test is requested but because of laboratory staff shortages, there is usually a delay of 3-4 weeks before PCR results are received.

1. **Does the child meet the criteria required for the WHO presumptive HIV diagnosis?**
   Yes, the child is less than 18 months old, has a positive HIV antibody test and has two symptomatic criteria, i.e. oral thrush and severe pneumonia.
2. **Discuss the selection of empiric antimicrobial therapy for the child.**
   HIV-associated pneumonia is caused by a wide spectrum of microorganisms. Polymicrobial pneumonia is common. Therefore, in severe pneumonia, empiric antimicrobial therapy should be broad-spectrum directed against common viruses (including CMV infection) and bacteria, and *Pneumocystis jirovecii*.
3. **In treating the pneumonia, which other management principles should be considered?**
   Appropriate respiratory support, maintain optimal fluid and electrolyte homeostasis, ensure adequate nutritional intake.
4. **Should the child be screened for tuberculosis?**
   Yes, tuberculosis should be excluded in all children with HIV infection and respiratory infection. Up to 10 percent of HIV-associated pneumonia may be caused by *M. tuberculosis*.
5. **Should ART be started in this infant?**
   Yes, the patient is less than 12 months old and meets the clinical criteria for a presumptive HIV diagnosis.
6. **When should ART be started?**
   ART should be commenced as soon as possible, after pre-ART initiation counseling has been completed and the baseline bloods have been taken, unless there is a medical reason which prevents the administration of ART, e.g. suspension of oral intake for a gastrointestinal problem, or markedly elevated liver function test results. Ideally, ART should be started within 2 weeks of confirming the HIV diagnosis. Because the HIV diagnosis was based on presumptive criteria, once the HIV DNA PCR result is available the management can be reviewed, if necessary.

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5.4

Prevention of Opportunistic Infections and Other Infectious Complications of HIV in Children

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Prevention of Opportunistic infections (OI) is a critical component of the care for HIV infected children, especially in developing countries with a large cesspool of community pathogens and limited availability of Highly Active Antiretroviral Therapy (HAART). Effective antiretroviral therapy with consequent immune reconstitution has substantially reduced the incidence and severity of most OIs, independent of the use of specific prophylactic measures.[1] However, it does not replace the need for OI prophylaxis in children with severe immune suppression. In fact, Immune Reconstitution Inflammatory Syndrome (IRIS) can unmask or complicate many OIs after initiation of antiretroviral therapy.

Timely initiation of prophylaxis against opportunistic infections is more important in HIV infected children than in adults as: a) OI in perinatally HIV infected children usually occurs after the child's immune system might already be compromised, b) OIs in HIV infected children often reflect primary infection rather than reactivation of prior infection, with possibility of delayed diagnosis and more virulent course.

Microbial Spectrum of OIs in Children

Microbial spectrum of OIs in HIV infected children is endless, though the frequency of different opportunistic pathogens among HIV infected children varies in different geographical regions. While some common infections in developing countries, e.g. tuberculosis and malaria are rarely seen in HIV infected children of developed countries, others, e.g. histoplasmosis or coccidiomycosis are limited to defined geographical regions. Some OIs, unlikely to be rare, have been never or rarely reported from resource-poor countries due to limited diagnostic facilities.

Relative frequency of OI pathogens in HIV infected children also varies with age, immunological status and history of previous OI.[2] Early institution of effective HAART therapy has markedly altered the frequency and course of most opportunistic infections, especially in developed countries. Some OIs, e.g. *Pneumocystis carinii* pneumonia (PCP) are more common in infants and young children. Infections like varicella-zoster (VCZ) often have different clinical presentations in young children (chickenpox) than in older children and adults (herpes zoster). History of a previous AIDS-defining OI is a predictor of developing similar new infection. Although majority of OIs occur in children who were substantially immunocompromised, serious bacterial infections, herpes zoster and tuberculosis occur across the spectrum of immune status.

Data regarding frequency of OIs in Indian HIV infected children are very limited and usually pertains to the children who were not on antiretroviral therapy.[3-9] Five most common reported OIs in Indian children are: Recurrent or serious bacterial infections, tuberculosis, candidiasis, PCP and VCZ. Cytomegalovirus (CMV) disease, toxoplasmosis and cryptosporidiosis have been occasionally reported, while *Mycobacterium avium complex* (MAC) infections are almost unknown.

On the other hand, commonly reported OIs in children of developed countries during pre-HAART era were: Serious bacterial infections, PCP, candidiasis, VCZ and MAC. Less commonly observed OIs (event rate <1.0 per 100 child-years) included CMV disease, cryptosporidiosis, TB, systemic fungal infections and toxoplasmosis.[1,10]

General Considerations in OI Prophylaxis

Immune-preservance and immune-restoration with early initiation of effective HAART regimens is the key intervention that has shown a dramatic drop in OIs-related morbidity and mortality in HIV infected children. In a

multi-centric observational study, the incidence of the most common initial OIs in children in the potent HAART era (2000-04) was substantially lower than the incidence in children followed at the same sites during the pre-HAART era (1988-98).[2,10] However, all OIs cannot be prevented with HAART alone and the need for effective OI prophylaxis cannot be overemphasized, especially in developing countries due to limited reach of HIV-population for antiretroviral therapy.

While dealing with issue of OI prophylaxis in HIV infected children, following interventions need due consideration with respect to feasibility, efficacy and safety:

a. ***Exposure prevention,*** i.e. avoidance or minimization of the exposure to opportunistic pathogens through public health measures and counseling of caretakers. Exposure prevention is the most costeffective intervention to prevent OI not only in HIV infected children but also in their contacts, reducing community reservoirs of infection. However, in developing countries, e.g. India with poor environmental conditions and health-ignorance, these measures are, at best, bound to have only limited success.
b. ***Primary prophylaxis*** (Table 5.4.1) against common OIs with appropriate antimicrobial agents is known to substantially reduce the associated morbidity and mortality, even in children who are not on antiretroviral therapy. However, issues, e.g. adherence, adverse events and drug interactions need due consideration before selecting an appropriate approach. Various recommendations are available for guidance regarding when to start, what to start and when to stop primary antimicrobial prophylaxis in HIV infected children and adolescents.[11,12]
c. ***Secondary prophylaxis*** (Table 5.4.2) after a documented attack of specific OI to prevent reinfection or reactivation of infection is equally important, as most OIs tend to recur in the same patient with higher frequency. Various recommendations regarding when to start, what to start and when to stop secondary antimicrobial prophylaxis in HIV infected children are also available.[11,12]

This chapter deals with certain issues related to preventive interventions against common OIs in HIV infected children with special reference to resource-limited settings in developing countries like India.

Serious or Recurrent Bacterial Infection

Serious or recurrent bacterial infections are leading opportunistic infections in HIV infected children, commonest being pneumonia, bacteraemia and meningitis. Minor infections, e.g. otitis media and sinusitis are more common than serious infections but often remain unnoticed or unreported. Bacterial infections are common in these children even with relatively preserved or restored immune status after antiretroviral therapy.

Microbiology of bacterial infection in HIV infected children depends on the site and source of infection. *Strept. pneumoniae* and *H. influenza type b* (Hib) are most common pathogens for community-acquired pneumonia in these children, who are also at higher-risk of developing invasive disease and death following them than non HIV children. *Strept. pneumoniae* is the commonest invasive gram-positive pathogen in children with HIV infection accounting for over 50 percent cases of bacteremia, followed by coagulase-negative staphylococci, *S. aureus* and enterococci.

Gram-negative bacteraemia is less common in HIV infected children, mainly seen in children with advanced immunosuppression or with central venous catheters. These children have higher-risk of gram-negative bacteremia due to *Pseudomonas aeruginosa*, nontyphoidal *Salmonella* and *E. coli* infections. HIV related immune dysfunction may also increase the risk of invasive meningococcal disease in HIV infected patients, but few cases have been reported.

Clinical presentation of bacterial infections in HIV infected children is generally similar to that in non HIV children, though common indicators, e.g. fever and leukocytosis might be absent in immunocompromised children. Mortality and recurrence of serious infections, e.g. pneumonia and meningitis is also more common in HIV infected children. One-third of HIV infected children with pneumonia have recurrence if not on antiretrovirals, though those with pre-existing lung damage have frequent recurrence even if started on HAART.

Isolation of a pathogen from normally sterile sites, e.g. blood, cerebrospinal fluid, pleural fluid, etc. is the gold standard for ***diagnosis*** of bacterial infections, which should always be followed by sensitivity testing due to rising incidence of resistant organisms, e.g. penicillin-resistant *S. pneumoniae* and methicillin-resistant *S. aureus*. Antigen assays or molecular biology techniques are useful for early or more accurate diagnosis, especially to detect unusual pathogens.

Exposure prevention to bacterial pathogens in HIV infected children is difficult and involves similar hygienic measures as for general population, e.g. avoidance of visits to crowded places and consumption of raw/undercooked or street foods. Even the caretakers of these children should take similar precautions to avoid being the reservoir or source of infection. Routine use of pneumococcal and Hib vaccines in US has dramatically reduced the incidence of vaccine-type invasive disease and colonization in the community, conferring herd protection to HIV infected children.

Primary prophylaxis against bacterial infections in HIV infected children involves appropriate immunizations against common pathogens, supported by selective use of IV immunoglobulins (IVIG) and co-PCP prophylaxis that also offers protection against bacterial infections.

All under-five HIV infected children should be immunized with the Hib vaccine with age-appropriate schedules, while it might be considered even in older children who have not received it previously.[11]

Safety and efficacy of pneumococcal vaccination in HIV infected population is generally well-established. Although, a placebo-controlled trial in adults reported higher-risk of pneumonia in HIV infected population following pneumococcal vaccination,[13] most studies have shown distinct benefits with substantially lower-risk of invasive pneumococcal disease after pneumococcal vaccination.

Efficacy of pneumococcal conjugate vaccine (PCV) in HIV infected children aged ≥ 5 years is controversial. In a placebo-controlled trial of 9-valent PCV, vaccine efficacy was lower in HIV infected versus noninfected children (65% vs 85%) but the incidence of invasive disease was substantially decreased in HIV infected vaccine recipients.[14] A multi-center study of HIV infected children not vaccinated with PCV in infancy has unequivocally shown the safety and immunogenicity of two doses of PCV followed by one dose of pneumococcal polysaccharide vaccine (PPV) in HAART-treated HIV infected children aged 2 to 19 years.[15]

As a general recommendation,[11] all HIV infected children aged 2-59 months should receive the (PCV) with age-appropriate schedules. Additionally, children aged >2 years should also receive the 23-valent PPV at least two months after the last PCV dose, with single revaccination after 3 years (if child is ≤10 years old) or after 5 years (in older children). All HIV infected adolescents with CD4 count >200 cells/mm^3 should receive a single dose of PPV unless received it in last five years. Even those with lesser CD4 counts can be offered PPV, though the clinical evidence has not confirmed efficacy in this group.

Although the efficacy of conjugated or polysaccharide meningococcal vaccine in HIV infected patients is unknown, it is recommended that at least the HIV infected children with other risk factors, e.g. asplenia, complement deficiency, etc. must receive meningococcal vaccine.

Since influenza increases the risk of secondary bacterial respiratory infections, inactivated influenza vaccine is recommended annually to all HIV infected children. Live attenuated influenza vaccine is contraindicated in HIV infected persons.

In the pre-HAART era, IVIG was recommended to prevent serious bacterial infections in symptomatic HIV infected children, but benefits were demonstrated only in those who were not on PCP prophylaxis with cotrimoxazole.[16] IVIG is no longer recommended for primary prevention of serious bacterial infections in HIV infected children unless hypogammaglobulinemia or functional antibody deficiency is present.[11]

Cotrimoxazole, used for PCP prophylaxis or azithromycin with/without atovaquone used for PCP or MAC prophylaxis has been shown to be effective in reducing the rate of serious bacterial infections in HIV infected children not on HAART.[17] However, indiscriminate use of antibiotics might promote resistant organisms and antibiotic prophylaxis is not recommended solely for the purpose of primary prophylaxis against serious bacterial infections.

In developing countries, supplementation with vitamin A and zinc has been shown to confer additional protection against bacterial diarrhea or pneumonia in HIV infected children.[18]

Secondary prophylaxis to prevent recurrence of serious bacterial infections in HIV infected children involves review of the immunization status against Hib, pneumococci, meningococci and influenza, discussed earlier. Cotrimoxazole or azithromycin prophylaxis given for PCP or MAC in these children also reduces the incidence of recurrent serious bacterial infections. Antibiotic prophylaxis to HIV infected children with frequent recurrences of serious bacterial infections may be considered but cautiously, due to the potential for development of resistant organisms. Rarely when antibiotic prophylaxis is not effective to prevent recurrence of serious bacterial infections (>2 attacks in one year), IVIG prophylaxis with 400 mg/kg every 2-4 weeks can be considered for secondary prophylaxis. Secondary antimicrobial prophylaxis may be stopped after adequate immune reconstitution following HAART. It has been demonstrated that discontinuation of MAC and/or PCP antibiotic prophylaxis in HIV infected children who achieved immune reconstitution (CD4 >15%) on antiretroviral therapy did not result in excessive rates of serious bacterial infections.[11]

Mycobacterium Tuberculosis

Tuberculosis is one of the commonest coinfection in HIV infected Indian children, present in ~ 30-50 percent cases. Studies have documented increased risk for Tuberculosis disease in HIV infected children even in developed countries where tuberculosis is uncommon.

Children are almost always infected via droplet infection from adult contact, though congenital tuberculosis is not uncommon in infants of HIV-TB coinfected women. Disease following BCG vaccination has also been reported.[19] Manifestation of tuberculosis

disease after starting antiretroviral therapy, due to IRIS, is well-known in children with latent infection.

Higher incidence of tuberculosis in HIV infected children reflects higher incidence of disease in their adult contacts (often also HIV infected) as well as higher-risk of progressive primary disease or reactivation of infection due to immunocompromised status. Unlike other OIs, CD4 count is not a reliable indicator of increased risk of tubercular disease in HIV infected children. Rising frequency of drug-resistant tuberculosis is another concern that has not only increased the adult sources of infection in endemic regions but has also made the treatment of coinfected children unsatisfactory with higher morbidity and mortality.

Clinical presentations of tuberculosis in HIV infected children are similar to those in non-HIV children, though disease tends to be more severe with higher-risk of miliary disease and meningitis. Extrapulmonary or disseminated tuberculosis is more common in HIV infected than in non-HIV children. Presentation of active disease is also influenced by the degree of immunodeficiency. In severe or advanced HIV disease, chest radiographs and histopathological findings might be markedly minimal despite severe disease. In these cases, tubercular infection may also be subclinical that might be unmasked after initiation of ART due to IRIS resulting in pronounced inflammatory reactions at the sites of infection.

Demonstration of acid-fast bacilli in infected body fluids or tissues is the gold standard for ***diagnosis*** of active tubercular disease, though with problems of appropriate sample collection and lower bacillary load in children make it difficult to apply.

Tuberculin test (TT) is the most useful way to detect tubercular infection, even latent, in children despite limitations. In HIV infected population, ≥5 mm of induration is considered as positive.[11] However, HIV infected children are more likely to have false-negative TT and a negative result should never be relied upon to exclude possibility of tubercular infection. Some workers recommend retesting of TT-negative cases with severe immunosuppression after achieving CD counts >15 percent on antiretroviral therapy. *Ex vivo* assays to determine IFN-γ release from lymphocytes after stimulation by highly specific synthetic *M. tuberculosis* antigens, though more specific than TT are also less sensitive in advance HIV disease and not routinely recommended for diagnosis of tubercular infection in HIV infected children.

In absence of bacteriological confirmation, diagnosis of active tuberculosis in HIV infected children often rests on constellation of indirect indicators, e.g. clinical suspicion, contact history, positive tuberculin test and abnormal radiograph or physical findings.

As most children do not have culture-proven disease and source cases may have a delay in the diagnosis of drug resistance, MDR-TB should be suspected in children with TB disease in the following situations:[20]

- Close contact with an MDR-TB patient
- Contact with a TB patient who died on treatment with reasons to suspect MDR disease, e.g. contact with another MDR-TB case, poor adherence to treatment or received >2 courses of antituberculosis treatment
- Bacteriologically proven TB with no response to first-line therapy under observation
- Exposure to source case who remain positive after 2 months of DOTS
- Children born in/exposed to residents of high prevalent regions for MDR-TB.

Exposure prevention involves avoidance of contact with an adult case, usually in the household. HIV infected children often have family members dually infected with HIV and TB. Homeless or institutionalized children are at higher-risk to contract the infection. Early detection and treatment of latent or active tubercular disease in household contacts is most important tool to reduce the risk of exposure for HIV infected children.

Primary prophylaxis to prevent development of active tubercular disease following infection involves BCG vaccination, early diagnosis of latent infection and preventive chemoprophylaxis.

BCG vaccine, despite controversial efficacy, is known to reduce the risk of severe tubercular disease following tubercular infection. However, there is also a potential risk of disseminated tubercular disease after live BCG vaccination, especially in immunocompromised children. Considering the high disease burden in developing countries like India and the fact that this vaccine is routinely given at birth when perinatally HIV-exposed children are unlikely to be immunocompromised, BCG vaccination is recommended to all infants born to seropositive mothers at birth. However, older children with symptomatic HIV infection or lower CD4 counts should not be BCG vaccinated. BCG vaccine is not routinely administered or recommended in the low-risk countries, e.g. United States.

Early diagnosis of latent tubercular infection in HIV infected children is important due to high-risk of disease progression and well-documented benefits of chemoprophylaxis. All HIV infected children should undergo Tuberculin testing at three months of age or at the time of HIV diagnosis, followed by re-testing at least once per year.

All asymptomatic HIV infected children with positive TT or contact with a contagious adult case should be treated for latent tubercular infection after excluding

active disease[21] with isoniazid (10-15 mg/kg/d or 20-30 mg/kg twice a week) for 6-9 months. A shorter 3-month regimen of isoniazid and rifampin has demonstrated equivalence to a 6-9 month isoniazid monotherapy but with better adherence.

The issue of preventive chemotherapy in HIV infected children of TB endemic regions with negative TT or no known contact is under exploration. A randomized, double-blind, controlled trial of isoniazid in HIV infected South African children was halted when isoniazid recipients were found to have reduced mortality than non-recipients, across all age-groups, CDC-HIV disease staging and TT results.[21] These results suggest that HIV infected children in high TB-burden areas may benefit from preventive isoniazid therapy irrespective of known exposure.

Although there are concerns that liberal use of isoniazid monotherapy may promote drug resistance, the problem is less real in children who generally have paucibacillary disease and contribute little to disease transmission. Isoniazid monotherapy in adolescents definitely increases the risk of acquired drug resistance due to high bacillary load with consequent risk of transmitting MDR-TB.

Secondary prophylaxis to prevent recurrence of tubercular disease is not recommended as the risk of recurrence is rare in children with drug-susceptible TB who are treated under direct observation. However, exogenous reinfection or endogenous relapse is possible. If HIV infected children, who were previously treated for latent/active tuberculosis, come in contact with a contagious case again, they should be retreated for presumed latent infection after excluding current disease. If active tuberculosis disease recurs, the child is at higher-risk of drug resistance and should be managed accordingly.

Mycobacterium Avium Complex (MAC) Disease

MAC was once the second commonest OI in HIV infected American children, though the incidence has substantially declined in recent years after widespread use of HAART. MAC infections have been very rarely reported in Indian HIV infected children.

MAC refers to many related species of nontuberculous mycobacteria, commonest being *M. avium* and *M. intracellulare*. *M. avium* is responsible for >95 percent cases of disseminated MAC disease in HIV population. These pathogens are ubiquitous and infection is acquired by routine exposure via inhalation, ingestion or inoculation. Person-to-person transmission is very rare.

In HIV infected children, MAC infection is rare during infancy and frequency increases with age and declining CD4 count. Disseminated MAC disease is rare in adults with CD4 >50 cells/mm^3, but children might suffer at much higher CD4 counts. High plasma HIV RNA load and colonization of respiratory/gastrointestinal tract with MAC are other risk factors for disseminated MAC disease.

Clinically, MAC is typically a disseminated disease in HIV infected children who are not on ART, presenting with unexplained fever, weight loss, gastrointestinal upsets, lymphadenopathy and hepatosplenomegaly. Respiratory symptoms are uncommon and isolated pulmonary disease is rare. Localized disease with lymphadenitis, pneumonitis, pericarditis, osteomyelitis or soft tissue abscesses is rare in childhood but being increasingly reported in children on antiretroviral therapy. MAC disease may also manifest as IRIS in cases with advanced immunosuppression after starting HAART.

Diagnosis of disseminated MAC disease rests on compatible clinical features coupled with isolation of MAC from cultures of blood, lymph node, bone marrow, or other tissue/body fluids. Presence of macrophage-containing acid-fast bacilli in histology specimens strongly indicates MAC in a suspected patient, but culture is essential to differentiate it from *M. tuberculosis* and for drug susceptibility testing.

Exposure prevention is difficult as MAC is a ubiquitous pathogen that commonly contaminate environmental sources, e.g. food and water. Available information does not support specific recommendations regarding avoidance of exposure. Person-to-person transmission is very rare.

Primary prophylaxis: Most effective way to prevent disseminated MAC in HIV infected children is to preserve immune functions with effective antiretroviral therapy.

Primary prophylaxis with Azithromycin (PO 20 mg/kg/week or 5 mg/kg/day) or Clarithromycin (PO 7.5 mg/kg twice daily) is indicated in HIV infected children with advanced immunosuppression according to the age-related CD4 count thresholds (Table 5.4.1).[11] Both these drugs also confer protection against respiratory bacterial infections. Rifabutin (PO 300 mg daily) is an alternative prophylactic agent for MAC disease in adults who cannot tolerate azithromycin or clarithromycin, but data on pediatric population is not available.

Before the prophylaxis is initiated, child should be evaluated for disseminated MAC disease, including blood culture. Detection of MAC in stool or respiratory tract may precede disseminated disease, but available data does not support initiating prophylaxis in patients with detectable organisms at these sites in the absence of positive blood culture and routine screening of respiratory or gastrointestinal specimens for MAC is not recommended.

Primary prophylaxis can be discontinued in HIV infected children, provided the child: a) is above 2 years of age, (b) has received HAART for ≥6 months and

Table 5.4.1: Primary prophylaxis against common opportunistic infections in HIV infected children

Pathogen	*When to start, stop and restart*	*Drug of choice*	*Alternatives*
PCP	***When to start*** • All infected/indeterminate infants <12 months • HIV infected children (age 1-5 years) with CD4 count <500 or <15% • HIV infected children (age > 6 years) with CD4 count <200 or <15% ***When to stop*** • Age >1 year • Completed 6 month of HAART • CD count >15% or 500 for 3 months (age 1-5 years) • CD count 15% or >200 for 3 months (age >6 years) ***When to restart*** • CD4 counts drop below above levels	PO TMP-SMX 150/750 mg/m^2/day as 2 divided doses 3 times/week on consecutive days *or* single dose 3 times/week on consecutive days *or* 2 divided doses daily *or* 2 divided doses 3 times/week on alternate day	PO dapsone 2 mg/kg/d or 4 mg/kg/week ***or*** PO atovaquone 30 mg/kg/d (age <4 months) 45 mg/kg/d (Age 4-24 months) ***or*** Aerosolized pentamidine 300 mg/mo (age <5 years)
MAC	***When to start*** • CD4 <50 (age ≥ 6 years) or <75 (2-5 years) or <500 (1-2 years) or <750 (<1 year). ***When to stop*** • Age >2 year • Completed 6 months of HAART • CD count >200 for 3 months (age 2-5 years) • CD count >100 for 3 months (age > 6 years) ***When to restart*** • CD4 counts drop below critical levels	PO clarithromycin 7.5 mg/kg/dose BD ***or*** PO azithromycin 20 mg/kg/week or ***or*** PO azithromycin 5 mg/kg/d	PO rifabutin 300 mg/d (age ≥6 years)
VZV	***When to start*** • Exposure to varicella or shingles with • No Past h/o varicella, zoster or vaccination or • Seronegative with reliable antibody test	IM VZIG 125 IU/10 kg (max 625 IU) within 96 hrs of exposure	PO acyclovir 20 mg/kg/dose QID x 5-7 days (VZIG not available or >96 hrs passed since exposure), ***or*** IVIG 400 mg/kg single dose within 96 hours of exposure
Toxoplasma	***When to start*** • IgG seropositive for *Toxoplasma* • CD4 counts <15 percent (age 2-5 years) • CD4 counts<100 (age > 6 years) ***When to stop*** • Age >1 year • Completed 6 months of HAART • CD4 counts >15 percent for 3 months (age 1-5 years) • CD4 >15% or >100-200 for 3 mo (age >6 years) ***When to restart*** CD4 counts drop below critical levels	PO TMP-SMX 150/750 mg/m^2/day as 2 divided doses 3 times/week on consecutive days *or* single dose 3 times/week on consecutive days *or* 2 divided doses daily *or* 2 divided doses 3 times/week on alternate day	PO dapsone 2 mg/kg or 15 mg/m^2/d + PO pyrimethamine, 1 mg/kg/d + PO leucovorin 5 mg every 3 days or PO atovaquone 30 mg/kg/d (age <4 months) 45 mg/kg/d (age 4-24 months) *with or without* PO pyrimethamine 1 mg/kg/d + PO leucovorin 5 mg every 3 days
Invasive bacterial infections	**When to start** Hypogammaglobulinemia (IgG <400 mg/dl)	IVIG 400 mg/kg every 2 to 4 weeks	
CMV	**When to start** • CMV antibody positive • CD4 counts <50	PO valganciclovir 900 mg/d with food (in childen who can receive adult dosing)	

Table 5.4.2: Secondary prophylaxis for common opportunistic infections in HIV infected children

Indication	*Drug of choice*	*Alternatives*	*When to stop and restart*
PCP (Prior attack)	PO TMP-SMX 150/750 mg/m^2/day as 2 divided doses 3 times/week on consecutive days *or* single dose 3 times/week on consecutive days *or* 2 divided doses daily *or* 2 divided doses 3 times/week on alternate days	PO dapsone 2 mg/kg/d or 4mg/kg/week *or* PO atovaquone 30 mg/kg/d (age <4 months) 45 mg/kg/d (age 4-24 mo) *or* Aerosolized pentamidine 300 mg/months (age <5 yrs)	***When to stop*** • Completed 6 months of HAART • CD4 >15% or 500 for 3 months (age 1-5 year) or • CD4 %>15% or 200 for 3 months (age >6 year) ***When to restart*** CD4 counts drop < above levels or PCP recurrence
Toxoplasma encephalitis (Prior Attack)	PO sulfadiazine 85-120 mg/kg/d in 2-4 divided doses + PO pyrimethamine, 1 mg/kg/d or 15 mg/m^2/d + PO leucovorin 5 mg every 3 days	PO clindamycin 20-30 mg/kg/d in 3-4 divided doses + PO pyrimethamine 1 mg/kg/d + PO leucovorin 5 mg every 3 days or PO atovaquone 30 mg/kg/d (age <4 months) 45 mg/kg/d (age 4-24 months) *with or without* PO pyrimethamine 1 mg/kg/d + PO leucovorin 5 mg every 3 days	***When to stop*** • Completed 6 months of HAART • Completed toxoplasma Rx • Asymptomatic for toxoplasma • CD4 >15 percent for 3 months (age 1-5 year) or CD4 >15 percent or 200 for 3 months (age >6 year) ***When to restart*** CD4 counts drop < above levels
MAC (Prior disease)	PO Clarithromycin, 7.5 mg/kg/dose BD+ PO Ethambutol 15-25 mg/kg/d ***With/without*** PO Rifabutin 5 mg/kg/d	PO azithromycin 5 mg/kg/d + PO ethambutol 15-25 mg/kg/d ***With/without*** PO rifabutin 5 mg/kg/d	***When to stop*** • Completed 6 months of HAART • Completed 12 months of MAC Rx • Asymptomaic for MAC • CD4 >200 for 6 months (age 1-5 year) or • CD4 >100 for 6 months (age >6 year) ***When to restart*** CD4 counts drop < above levels
CMV (Prior retinitis or neurologic disease or GIT disease relapse)	IV ganciclovir 5 mg/kg/d ***or*** IV foscarnet 90-120 mg/kg/d ***or*** PO valganciclovir 900 mg/d ***with*** periodic ophthalmic follow-up	(For retinitis) Ganciclovir SR implant every 6-9 months + PO ganciclovir 30 mg/kg TDS	***When to stop*** • Completed 6 months of HAART • Ophthalmologist clearance • CD4 >15 percent or 500 for 3 months (age 1-5 yr) • CD4 >100 for 3 months (age >6 year) ***When to restart*** • CD4 counts drop < above level • Relapse or IRIS uveitis
Cryptococcosis (Documented disease)	PO fluconazole 6 mg/kg/d	PO itraconazole 5 mg/kg/dose BD	***When to stop*** • Age > 6 years • Completed 6 months of HAART • Completed 6 months of prophylaxis • Asymptomatic for 6 months • CD4 >200 for 6 months ***When to restart*** CD4 counts drop < above levels
Coccidiomycosis (Documented disease, not routinely recommended)	PO fluconazole 6 mg/kg/d	PO itraconazole 2-5 mg/kg/dose BD	Not established

Contd...

Contd...

Histoplasmosis (Documented disease)	PO itraconazole 5 mg/kg/dose BD	PO fluconazole 3-6 mg/kg/d	***When to stop:*** • Age >6 yrs • Completed 6 mo of HAART • Received 1 year of treatment • CD4 >150 or 15%. • Negative blood culture • Serum antigen <2 ngm/l ***When to restart*** CD4 counts drop < above levels
Microsporidiosis (Disseminated, non-ocular infection by microsporidia other than *E.bieneusi*, ocular infection)	PO albendazole 7.5 mg/kg/dose BD	PO albendazole 7.5 mg/kg/dose BD with topical drugs for ocular infections	Till immune reconstitution after initiation of HAART
Bacterial infections (>2 attacks in a year)	PO TMP-SMX 150/750 mg/m² In two divided doses *Or* IVIG 400 mg/kg/ 2-4 weeks	Antibiotic chemoprophylaxis with another active agent	Not established
Candida (Esophageal or Frequent/Severe recurrences)	PO fluconazole 3-6 mg/kg/d	None	Not established
HSV (Frequent/ Severe recurrences)	PO Acyclovir 20 mg/kg/dose BD	PO valacyclovir 500 mg BD or PO famciclovir 500 mg BD* (*for children old enough to receive adult dosing)	Not established

(c) has shown sustained CD4 count recovery for >3 months above the age-specific targets, i.e. >100 cells/mm³ in children ≥6 years and >200 cells/mm³ in children aged 2-5 years. MAC prophylaxis should not be discontinued in children below two years of age. Primary prophylaxis should be reintroduced if the CD4 count drops below the above mentioned threshold.[11]

In a study of discontinuing MAC prophylaxis in HIV infected children on HAART with CD4 counts ≥20 percent (>6 years age) or ≥25 percent (2-6 years age) no MAC events were observed on two years follow-up in 63 children after discontinuation of MAC prophylaxis.[22]

Secondary prophylaxis for life is recommended to all cases with history of disseminated MAC to prevent recurrence. However, based upon immune reconstitution data in adults and data in children discontinuing primary prophylaxis, some experts recommend discontinuation of secondary prophylaxis in HIV infected children, provided the child (a) is above 2 years of age, *(i)* has completed at least 12 months of MAC treatment, *(ii)* has remained asymptomatic for signs and symptoms of MAC and (b) has received HAART for ≥6 months and (c) has shown sustained CD4 count recovery for >3 months above the age-specific targets, i.e. >100 cells/mm³ in children ≥6 years and >200 cells/mm³ in children aged 2-5 years.[11] Secondary prophylaxis should be reintroduced if the CD4 count falls below the above mentioned threshold.

Pneumocystis Pneumonia (PCP)

PCP is a major cause of morbidity and mortality in young HIV infected children, but the incidence had shown exemplary decline with specific chemoprophylaxis even during pre-HAART era. CDC data indicate a progressive decline in PCP infection rates as cases per 1,000 HIV infected children from 25 in 1994 to 18 in 1996 and 6 in 2001.[2] Incidence has shown a further sharper decline in HAART era.[3-4] PCP has contributed to 5-8 percent on all reported OIs in Indian HIV infected children.[3-9]

PCP is caused by *Pneumocystis jirovecii*, a ubiquitous organism infecting humans (*Pneumocystis carinii* now refers only to the pneumocystis that infects rodents). Although the mode of infection is not firmly established, human-to-human transmission most likely occurs via airborne route. In one report, one of the eight infants born to HIV infected women with PCP during pregnancy had evidence of *Pneumocystis* infection, suggesting possibility of intrauterine transmission.[23]

Pneumocystis infection usually occurs in early childhood and two-thirds of healthy children have antibodies against *P. jirovecii* by the end of preschool years. Infection is generally asymptomatic and PCP disease occurs almost exclusively in immunocompromised host, either after new acquisition of infection or reactivation of latent infection. Maximum cases of PCP occur in the first year of life of HIV infected children with peak at 3-6 months. Low CD4 counts <14 percent is the most important risk factor for PCP in HIV infected children, apart from high plasma HIV RNA levels and previous episode of PCP or other OIs.

Clinically, PCP presents as acute or sub-acute pneumonia with progressive hypoxia. Chest skiagram may reveal diffuse, bilateral, symmetrical *butterfly* interstitial infiltrates or *ground-glass appearance*, but a normal X-ray does not exclude PCP. Extrapulmonary *Pneumocystis* organisms are found in <2.5 percent of HIV infected children with or without concurrent PCP, located at multiple noncontiguous sites, especially gastrointestinal tract.[24]

Diagnosis rests on clinical suspicion, low CD4 counts and progressive hypoxemia on blood gas analysis, confirmed by demonstration of the organisms on special staining in respiratory secretions or lung tissue. However, treatment can be initiated before definitive diagnosis as organisms persist in clinical specimens for days or weeks after effective therapy is initiated. Bronchoalveolar lavage is the procedure of choice for sample collection in young children, while transbronchial or open lung biopsy is recommended only in select cases. Nasogastric aspirates, if positive, are of diagnostic value. Many PCR assays for detection of human *Pneumocystis* are available but most of them are usually more sensitive but less specific. *Pneumocystis*-specific DNA is found in 18 percent of BAL samples from patients without clinical PCP or HIV disease.[25]

Exposure prevention is difficult and isolation of hospitalized PCP case is not required from individuals with normal immune responses or from immunocompromised high-risk patients on PCP prophylaxis. Though some authorities recommend that cases who are at risk for PCP should not share a hospital room with a PCP case, data are insufficient to support this recommendation.

Primary prophylaxis is the most effective means to prevent PCP in HIV infected children, recommended for: (a) All HIV infected infants <12 months regardless of CD4 count, (b) All HIV infected children between 1-5 years with CD4 counts <500 cells/mm^3 or <15 percent and (c) All HIV infected children ≥6 yrs with CD4 counts <200 cells/mm^3 or <15 percent.[11]

All infants born of HIV infected mothers should receive PCP prophylaxis from 4-6 weeks of age, including those with indeterminate HIV infection status until they are determined to be uninfected or presumptively uninfected with HIV. In nonbreastfed infants, *presumptive exclusion of infection* rests on: (a) two negative virologic tests at ≥2 weeks and ≥4 weeks of age, or (b) one negative virologic test at ≥8 weeks; or (c) one negative HIV antibody test at ≥6 months. *Definitive exclusion of HIV infection* is based on: (a) Two negative virologic tests at ≥1 month and ≥4 months of age, or (b) Two negative HIV antibody test results from separate specimens at ≥6 months. For both, presumptive and definitive exclusion of infection, the child should have no other virological or clinical evidence of HIV infection.[11]

Cotrimoxazole (trimethoprim+sulphamethoxazole or TMP-SMX) is the drug of choice for PCP prophylaxis due to high efficacy, relative safety, low cost and broad antimicrobial spectrum. Trimethoprim alone has little, if any, anti-*Pneumocystis* activity but enhances the activity of the sulfonamide. Prophylactic dose is 150 mg/m^2 TMP and 750 mg/m^2 SMX (5 mg/kg/d TMP and 25 mg/kg/d SMX) given orally in two divided doses daily or three consecutive or alternate days in a week. For patients with impaired renal function, a reduced dose may be necessary.

TMP-SMX is also effective in the prevention of toxoplasmosis and some bacterial infections, e.g. *Salmonella, Hemophilus, Staphylococcus* and others.

Dihydropteroate synthase (DHPS) gene mutations in *Pneumocystis* from humans have been observed with TMP-SMX suggesting possible drug resistance, but studies for clinical correlates have not provided conclusive results.[26] More important is the association of prolonged TMP-SMX prophylaxis for PCP with emergence of resistance for bacterial pathogens, a point to be considered in the management of bacterial infections in patients receiving prophylaxis.

Adverse events, e.g. rash is a major concern with TMP-SMX prophylaxis. Adult studies suggest that in cases with non-life-threatening adverse events, chemoprophylaxis with TMP-SMX should be continued, if clinically feasible or reinstituted after the adverse event has resolved. Patients with adverse events, e.g. fever and rash, might better tolerate reintroduction of the drug with a gradual increase in dose or reintroduction of TMP-SMX at a reduced dose or frequency.

In children who cannot tolerate TMP-SMX prophylaxis, second choice would be either atovaquone with/without azithromycin or dapsone. Both are equally effective but atovaquone is expensive while dapsone has serious adverse effects.

Atovaquone is administered with meals as a single oral dose of 30 mg/kg/d for infants <3 months and 45 mg/kg/d for those aged 4-24 months. Unlike TMP-SMX, atovaquone has no antibacterial activity but is effective against toxoplasma. Azithromycin in a single dose of 5

mg/kg/day has been used to supplement atovaquone for broader-spectrum prophylaxis. A double-blind study has shown atovaquone-azithromycin combination to be as effective as TMP-SMX for the prevention of serious bacterial infections as well as PCP.[27]

Dapsone may be given either daily (2 mg/kg/d) or weekly (4 mg/kg/wk) orally. It is as effective as atovaquone but slightly less effective than TMP-SMX.

For patients seropositive for *Toxoplasma gondii* who cannot tolerate TMP-SMX, recommended alternatives for prophylaxis against both PCP and toxoplasmosis include dapsone with pyrimethamine or atovaquone with/without pyrimethamine.

Aerosolized pentamidine may also be used in children who cannot take TMP-SMX, atovaquone, or dapsone prophylaxis, in a monthly dose of 300 mg irrespective of age. IV pentamidine is not recommended for prophylaxis.

Pyrimethamine-sulfadoxine combination, an effective prophylactic regimen in adults, carries high-risk of cutaneous reactions and has not been evaluated adequately in HIV infected children.

Studies on HIV infected children following immune reconstitution after HAART demonstrate acceptable low-risk for PCP after discontinuation of prophylaxis. Data from the PACTG 1008 study evaluated 235 HIV infected children and adolescents on antiretroviral therapy who received PCP prophylaxis ≥6 months and achieved CD4 percentages of ≥20 percent (for patients aged >6 years) and ≥25 percent (aged 2-6 years), after which the prophylaxis was stopped. In over two years follow-up, no cases of PCP occurred and only 9.4 percent cases required reinstitution of PCP prophylaxis.[22] Adult studies also indicate very low-risk of PCP after discontinuation of prophylaxis after adequate immune reconstitution is achieved with HAART.

Thus, PCP prophylaxis may be discontinued in HIV infected children, who have: (a) received HAART for ≥6 months and (b) achieved sustained rise in CD4 counts >15 percent with absolute count ≥200 cells/mm^3 (>6 years age) or ≥500 cells/mm^3 (1-5 years age) for >3 months. Subsequently, CD4 counts should be re-evaluated at least every 3 months and prophylaxis must be reinstituted, if the original criteria for prophylaxis are reached. PCP prophylaxis should not to be discontinued in HIV infected infants aged <1 year.[11]

Secondary prophylaxis: None of the drugs administered for the treatment and prevention of PCP eradicates *Pneumocystis* and prophylaxis is effective only till the selected drug is administered. Hence, all HIV infected children should continue secondary prophylaxis or chronic maintenance therapy for life after an attack of PCP, unless immune reconstitution occurs with ART. Drugs and dosage regimen used for secondary prophylaxis are similar to those used for primary prophylaxis.

Secondary prophylaxis may also be discontinued using the same criteria as for the discontinuation of primary prophylaxis, discussed earlier. Subsequently, the CD4 percentage and CD4 count should be re-evaluated at least every 3 months and prophylaxis must be reinstituted, if the original criteria for prophylaxis are reached or if PCP recurs. Secondary prophylaxis should not be discontinued in HIV infected infants.[11]

Individuals who present with clinical signs and symptoms compatible with PCP after discontinuation of prophylaxis should be evaluated thoroughly despite normal or high CD4 counts and if PCP recurs at a higher CD4 count than the limits mentioned earlier, lifelong prophylaxis should be continued.

Candida Infections

Candida are commensals on mucosal surfaces of health persons and infections due to *Candida* species, *albicans* and *nonalbicans*, are commonest fungal infections in HIV infected children, which may present as *localized* disease, e.g. oropharyngeal candidiasis, esophageal candidiasis, etc. or as *Invasive* disease with candidemia and disseminated candidiasis.

Localized candidiasis is almost always caused by *albicans species* and oropharyngeal candidiasis (OPC) is one of the most frequent OIs in HIV infected children reported in 30-40 percent cases at some point of time. Incidence of localized disease has declined dramatically in HAART era, mainly seen in children with: (a) CD4 count <200 cells/mm^3, (b) high viral load, (c) Neutropenia <500 cells/mm^3 and (d) Lack of effective HAART.

Invasive disease is more common in HIV infected children with indwelling venous catheters or esophageal coinfection with HSV or CMV, apart from risk factors for localized disease stated earlier. About half of the reported cases of *Candidemia* in HIV infected children are caused by *nonalbicans* species which are frequently resistant to antifungal azole compounds, posing management problems.[28]

Clinically, OPC present with painless, creamy white, curd-like lesions (thrush) on tongue or oropharyngeal mucosa, which can be easily scraped off to expose inflamed underlying mucosa. Uncommonly, these lesions may be atrophic or hypertrophic. Esophageal candidiasis presents with odynophagia, dysphagia, vomiting and retrosternal pain. Most of these cases have concomitant OPC. Children who develop esophageal candidiasis despite HAART therapy are less likely to have concomitant OPC. Invasive candidiasis may present with candidemia or disseminated disease with meningitis, endocarditis, renal disease, endophthalmitis and hepatosplenic disease. Delayed detection of invasive candidiasis is frequently fatal. New onset fever in a HIV

infected child with advanced disease and central venous catheter *in situ* is the commonest manifestation of candidemia with/without other manifestations.

Diagnosis of superficial candidiasis, e.g. OPC or diaper dermatitis can be made clinically, while laboratory confirmation requires microscopic examination of lesion scrapping for yeast forms using potassium hydroxide (KOH) preparation. For recurrent or refractory OPC, cultures with *in vitro* susceptibility testing can be used to guide antifungal treatment.

Presence of classic *cobblestone appearance* on barium swallow in a case of OPC is a reliable indicator of esophageal candidiasis, which can be confirmed visually on esophagoscopy and histopathologic demonstration of yeast forms in tissue and culture confirmation. Endoscopy also helps to exclude other causes of esophagitis, e.g. HSV, CMV, MAC, etc.

Diagnosis of invasive candidiasis is best made on blood cultures along with relevant investigations for end-organ involvement. New diagnostic tests such as the urine D-arabinitol/L-arabinitol ratio, serum D-arabinitol/creatinine ratio, *Candida* antigen mannan, β-D-Glucan assay and PCR are promising alternatives but none has been validated in children.

Exposure prevention to *Candida* is very difficult as these fungi are common commensals on mucosal surfaces in healthy individuals and no measures are available to reduce exposure.

Primary prophylaxis of candidiasis in HIV infected children is not routinely indicated, given the low prevalence of serious *Candida* infections in the HAART era, availability of effective treatment, potential risk of the development of resistant *Candida* strains, drug interactions between antifungal and antiretroviral agents and lack of randomized controlled trials in the pediatric population. However, adult data indicate that fluconazole can reduce the risk for mucosal candidiasis in patients with advanced HIV disease.

Secondary prophylaxis for recurrent OPC is also generally not recommended due to same reasons as for primary prophylaxis. However, if recurrences are severe, suppressive therapy with systemic azoles, either oral fluconazole (PO 3–6 mg/kg/day) or itraconazole, may be considered based on data in adults on HAART.[11] Potential for azole resistance should be considered when long-term prophylaxis with azoles is considered. A recent randomized trial in adults has documented significantly lower number of OPC episodes and other invasive fungal infections in HIV patients with CD4+ count <150 cells/mm^3 on continuous fluconazole versus episodic treatment of recurrences.[29] This clinical trial also proved that the development of significant resistance was not higher in the group of continuous prophylaxis than in the group with episodic administration of fluconazole, provided that patients are on antiretroviral therapy.

Based on adult data, children with fluconazole-refractory OPC or esophageal candidiasis who have responded to voriconazole or posaconazole therapy or echinocandins, continuing the effective drug as secondary prophylaxis may be considered because of high relapse rate until HAART produces immune reconstitution.

No data is available to recommend the duration of secondary prophylaxis but it would be reasonable, based on experience in HIV infected adults with other OIs, to discontinue secondary prophylaxis when the CD4 counts have exceeded CDC Immune Class 2 or 1.

Cryptococcosis

Cryptococcal disease is relatively rare in HIV infected children than in HIV infected adults and the incidence has substantially declined in recent years due to effective antiretroviral therapy.

Cryptococcal infections are caused by inhalation of aerosolized particles of *Cryptococcus neoformans* from the environment and infection is usually acquired in early childhood. Serologic studies of immunocompetent children indicate that most children are infected by the second year of life. Despite the high incidence of infection, cryptococcal disease is very rare in immunocompetent population and in HIV infected children, cryptococcal disease is mostly seen in 6-12 years age-group with severe immunosuppresion, i.e. CD4 counts <50 cells/mm^3.

Clinically, cryptococcosis in HIV infected children usually presents as sub-acute meningoencephalitis, evolving over few days or weeks. CNS mass lesions (cryptococcomas) have not been reported in children. Few cases may present with disseminated cryptococcosis involving skin and/or lungs with or without CNS disease. Asymptomatic disease with accidental detection of pulmonary nodules on routine chest radiograph is known.

Diagnosis generally rests on detection of serum or CSF cryptococcal antigen by latex agglutination test—a useful screening test positive in >90 percent cases. In cryptococcal meningitis, routine CSF examination is usually normal and CSF antigen test may be negative in some cases with very high/low titers or infection by nonencapsulated strains. Other methods of diagnosis include CSF microscopy with India-ink staining and culture. Blood culture is positive in ~75 percent cases of cryptococcal meningitis. Pulmonary and skin disease may be diagnosed by direct examination of India ink-stained specimens, culture and antigen detection from suitable samples.

Exposure prevention: Avoidance of cryptococcal infection is difficult, though epidemiologic evidence

suggests that activities, e.g. exposure to bird droppings, lead to higher-risk for infection.

Considering the very low incidence of cryptococcal disease, routine testing of asymptomatic children for serum cryptococcal antigen is not recommended.

Primary prophylaxis: A Cochrane Review of randomized clinical trials has shown reduced frequency of cryptococcal disease in adults with advanced HIV disease and severe immunosuppression after fluconazole and itraconazole prophylaxis.[30] However, none of these interventions showed clear effect on mortality and primary prophylaxis for cryptococcal disease is not recommended in children due to rarity of the disease and possibility of drug interaction and drug resistance.

Secondary prophylaxis: Children who have completed the initial therapy for acute cryptococcosis should be on chronic maintenance therapy to prevent the relapse. Fluconazole (PO 6 mg/kg/day) is superior and preferable to itraconazole (PO 5 mg/kg/day) and should be continued either life-long or until immune reconstitution occurs on ART.[11] Recent data suggests that secondary prophylaxis may be discontinued after 6 months in asymptomatic children who are on HAART and have reached a CD4 count of >200 cells/mm^3. Some workers prefer CSF examination for culture and antigen negativity before discontinuation of secondary prophylaxis even in asymptomatic cases. Secondary prophylaxis should be reinitiated if the CD4 count drops <200 cells/mm^3

Aspergillosis

Invasive aspergillosis is a rare but potentially lethal infection in HIV infected children and the incidence has further declined in HAART era.

Aspergillus species are ubiquitous molds, present widely in soil or decomposing organic materials and infection is acquired by inhalation of spores (conidia). Most cases of invasive aspergillosis are caused by *Aspergillus fumigatus*, rarely by A. *flavus*. Risk factors for invasive disease in HIV infected children include advanced immunosuppression (CD4 <100 cells/mm^3), neutropenia, prolonged antibiotic/steroid therapy, preexisting lung disease and no HAART.

Clinically, invasive aspergillosis usually presents as necrotizing pneumonia or laryngotracheobronchitis. Necrotizing pneumonia is the commonest form of invasive aspergillosis in HIV presenting with persistent fever, cough, dyspnea, pleuritic pain, hemoptysis and diffuse, focal or cavitary infiltrates on chest skiagram. A "halo" of low attentuation surrounding a pulmonary nodule or an "air-crescent" on CT lung is highly suggestive of disease. Laryngotracheobronchitis has more acute presentation with fever, cough, dyspnea and stridor or wheezing. Bronchoscopy may reveal multiple ulcerative or plaque-like lesions adherent to airways. Extrapulmonary forms of invasive aspergillosis include ENT infections, cutaneous disease and CNS disease as brain abscess or meningitis. Disseminated aspergillosis is rare.

Diagnosis depends on the demonstration of organisms (hyphae) in biopsy specimens from involved sites with positive culture. In absence of lung biopsy, presumptive diagnosis of pulmonary aspergillosis can be made in a clinically compatible case with: (a) repeated isolation of *Aspergillus* sp. on culture from respiratory secretions *or* (b) presence of dichotomously branching septate hyphae consistent with *Aspergillus* sp. in respiratory or other samples.

Exposure prevention: *Aspergillus* sp. are ubiquitous and exposure is unavoidable. Avoiding dusty environment, indoor plants/flowers and food items such as nuts/spices which are often contaminated with fungi is advisable. Hospital infection control measures include minimal use of nonsterile biomedical devices and adhesive tape and laminar air flow system in patient care area.

Primary prophylaxis for aspergillosis is not recommended in HIV infected children due to low incidence of invasive disease and unknown efficacy and safety of potential prophylactic agents. Low-dose amphotericin B, itraconazole or voriconazole prophylaxis has been used to prevent aspergillosis with unknown efficacy.

Secondary prophylaxis: In non HIV immunocompromised patients of aspergillosis, chronic maintenance therapy throughout the duration of immunosuppression seems to be associated with a more favorable outcome. However, no data is available in HIV infected populations and hence, secondary prophylaxis is currently not recommended.

Histoplasmosis

Histoplasmosis is a rare opportunistic fungal infection in HIV infected children outside the endemic regions of Ohio and Mississippi River Valleys in United States and in Latin America, caused by inhalation of microconidia produced by the mycelial form of *Histoplasma capsulatum*. Transplacental infection has rarely been reported.

Clinically, acute pneumonia and meningitis is the usual presentation in non HIV children or HIV infected children without advanced immunosuppression, while *progressive disseminated histoplasmosis* is more common in HIV infected children with CD4 counts ≤150 cells/ mm^3. Disseminated histoplasmosis presents with prolonged fever, failure to thrive, pneumonitis, hepatosplenomegaly and lymphadenopathy; and may be fatal if untreated.

Diagnosis rests on culture, histopathology, serology, antigen detection and molecular diagnostic techniques. Cultures, histopathology and molecular diagnosis with PCR and DNA probes are diagnostic but with poor sensitivity. Complement fixing antibody titers of ≥1:32 to the yeast and/or mycelial antigens are considered strongly suggestive of active or recent infection, though may be false negative in HIV infected persons. EIA can detect antigen in serum, bronchoalveolar lavage and CSF with nearly 100 percent sensitivity in children.

Exposure prevention: Avoidance of exposure is difficult in endemic regions, those with CD4 counts ≤150 cells/mm^3 should avoid visiting dusty environment, e.g. construction sites, areas contaminated with bird or bat droppings, etc. Protective respiratory devices may also reduce the likelihood of infection.

Primary prophylaxis with itraconazole is recommended for HIV infected adults of endemic region with CD4 count <150 cells/mm^3, but not in children due to low incidence of disease in HIV infected children, possibility of drug interaction and potential antifungal drug resistance.

Secondary prophylaxis is recommended in children after completion of initial amphotericin B treatment with oral itraconazole maintenance therapy (PO 5 mg/kg/dose twice daily) for at least one year. Longer suppressive therapy may be required in HIV infected children who are severely immunosuppressed (CD4 <15 percent or <150 cells/mm^3 in children ≥6 years) or who relapse despite appropriate therapy. Fluconazole (PO 3-6 mg/kg/d) is less effective than itraconazole and there is only limited experience in children with voriconazole.[11]

Discontinuation of secondary prophylaxis has not been adequately explored in children. However, based on adult data, it may be discontinued in children on HAART with immune restoration (CD4 >15 percent or >150 cells/mm^3 in children ≥6 years). Chronic suppressive therapy is recommended for patients who relapse despite appropriate treatment.[11,12]

Coccidioidomycosis

Coccidioidomycosis is a very rare opportunistic fungal infection in HIV infected children outside the endemic regions of Southwestern United States and parts of Central and South America. Infection results from the inhalation of spores of *Coccidioides immitis* and *C. posadasii*, present in soil or contaminated fomites. Cellular immunosuppression is a major risk factor for severe primary coccidioidomycosis or relapse of past infection and systemic disease is usually seen in cases with CD4 counts ≥100 cells/mm^3 or <15 percent.

Clinically, coccidioidomycosis in HIV infected children may be asymptomatic or present with localized pulmonary disease or disseminated disease involving meninges, lymph nodes and/or liver. Focal pneumonia is most common in those with CD4+ counts >250 cells/mm^3, whereas other syndromes usually occur in more immunosuppressed patients.

Diagnosis is confirmed by culture from clinical specimens or by demonstration of the typical spherule on histopathology of involved tissue. Coccidioidal IgM and IgG serology is useful in diagnosis though may be false negative in cases with low CD4+ counts. CSF culture is positive in <30 percent and a complement-fixation IgG antibody test in CSF is useful for diagnosis of meningitis.

Exposure prevention: Avoidance of exposure is difficult in endemic regions though HIV infected children should avoid activities involving extensive exposure to disturbed native soil, e.g. building excavation sites or dust-storms.

Primary prophylaxis for coccidioidial infections is not recommended in children, considering low incidence of disease and problems of drug resistance or drug interactions. Some experts recommend annual coccidioidal antibody testing in HIV infected patients of endemic region and primary prophylaxis with an azole, e.g. fluconazole to coccidioidal antibody-positive patients with CD4 <250 cells/mm^3 or history of thrush, till sustained rise of CD4 counts above this value for 6 months.[31] Routine antibody testing and primary prophylaxis outside the endemic region is not recommended.

Secondary prophylaxis by life-long antifungal suppression with either fluconazole (PO 6 mg/kg/day) or itraconazole (PO 2-5 mg/kg/dose twice a day) is recommended for HIV infected children with coccidioidomycosis, due to high-risk (~80%) of recurrence following disseminated coccidioidomycosis or coccidioidal meningitis even, if immune reconstitution is achieved with HAART.

Cytomegalovirus Disease

Cytomegalovirus disease is less frequent in HIV infected children than in HIV infected adults. CMV infection is acquired vertically from infected mother or horizontally via contact with infected breast milk, saliva, urine, blood transfusions, etc. Asymptomatic infections are common and in populations with high maternal seropositivity, >50 percent infants acquire it before one year.

HIV infected pregnant women not only have higher prevalence of CMV infection but also the higher frequency of viral shedding from the cervix.[32] Consequently, the risk for perinatal CMV transmission is higher in infants born to women dually infected with CMV and HIV.

Congenital infection usually occurs in infants born to the women with primary CMV infection during pregnancy, though recent studies indicate that *in utero* transmission can occur due to reactivation of previous infection or reinfection with a different strain. CMV can also be transmitted during peripartum period due to viral shedding in maternal secretions and breast milk, though symptomatic disease is uncommon in these babies. HIV infected children are at higher-risk to acquire CMV infection during early childhood than others, specially in infancy. Symptomatic HIV-CMV coinfected children also have 3-4 times higher frequency of CMV viruria than asymptomatic HIV infected/exposed children, thus being bigger source of infection to others.

Clinically, only ~10 percent of *in utero* CMV infections manifest at birth in non-HIV setting. However, babies with congenital CMV-HIV coinfection have accelerated progression of both diseases, specially if not on antiretroviral therapy. Symptomatic CMV disease in HIV infected children is mainly seen in cases with CD4 <100 cells/mm^3, though young infants can manifest at much higher, age-adjusted CD4 counts. Other risk factors include high viral load and history of previous OI.

Retinitis is the commonest manifestation of CMV disease in HIV infected children, which may be asymptomatic in young infants. Other important presentations include GIT disease (colitis, esophagitis, hepatitis), Pulmonary manifestations (interstitial pneumonia) and neurological disease (subacute focal encephalopathy, myelitis or polyradiculopathy).

Diagnosis of CMV infection by serology is unreliable in HIV infected infants due to transplacental transfer of antibodies. In older children, a positive CMV antibody titre, culture or PCR indicates CMV infection but not necessarily active disease. Diagnosis of active disease depends on a positive CMV culture or DNA-PCR from leukocytes, body fluids, e.g. CSF or tissues in a clinically compatible case. Quantitative DNA-PCR can be used as a marker of the risk for active disease and to monitor response to therapy. Recovery of virus from endoscopic biopsy specimens, e.g. colonic, esophageal or lung biopsies provides direct evidence of disease in symptomatic patients. Characteristic histopathology in biopsy specimens with *Owl's eye* intranuclear and intracytoplasmic inclusion bodies and positive staining for CMV antigens or monoclonal antibodies are also highly suggestive of CMV disease.

Exposure prevention: While primary CMV infection in mother during pregnancy is the commonest source of CMV infection in infants, risk for symptomatic disease in the fetus is low and treatment of asymptomatic maternal CMV infection during pregnancy solely to prevent infant infection is not indicated. Postnatal risk for acquiring CMV infection may be marginally reduced by optimal hygienic practices, e.g. handwashing. HIV-exposed/infected children who are seronegative for CMV should be administered only CMV antibody-negative or leukocyte-poor blood products, if needed.

Primary prophylaxis: Annual CMV antibody testing has been recommended beyond infancy for all CMV seronegative HIV infected children with CD4 counts <100 cells/mm^3 or 10 percent, to detect newly infected children who might benefit from screening for retinitis.

Primary prevention of severe CMV disease rests on early diagnosis of ophthalmic disease and prevention of severe immunosuppression by HAART. HIV infected children <5 years who are CMV infected and severely immunosuppressed (CD4 <50 or <5%) should undergo retinal examination every 6 months. Older children should be counseled to be aware of "floaters" in the eye and visual changes.

In the HAART era, CMV end-organ disease has diminished to such an extent that primary prophylaxis with antiviral agents, e.g. valganciclovir in HIV/CMV coinfected people is generally not recommended due to the cost, potential to induce CMV resistance and the lack of distinct survival advantage. CMV end-organ disease is best prevented by using antiretroviral therapy to maintain CD4 count >100 cells/mm^3. If it is not possible, valganciclovir prophylaxis (PO 900 mg/day with food) might be considered in HIV infected adolescents who are CMV-seropositive, have CD4 <50 cells/mm^3 and can take adult doses of valganciclovir.

Secondary prophylaxis is recommended for life in all cases of disseminated CMV disease after induction therapy unless immune reconstitution occurs after antiretroviral therapy, as CMV disease is not cured with available antiviral agents. The need of secondary prophylaxis for localized gastrointestinal disease or CMV pneumonitis is not well established.

For patients with retinitis, decisions should be made in consultation with an ophthalmologist, considering anatomic location of the retinal lesion, vision in the contralateral eye and the immunologic and virologic status of the patient. Ganciclovir (IV 5 mg/kg/day) or foscarnet (IV 90-120 mg/kg/day) are the preferred secondary prophylaxis regimens for children, while PO valganciclovir (PO 900 mg/day) can be considered for older children able to receive adult dosing. Repetitive intravitreous injections of ganciclovir, foscarnet and cidofovir are effective for secondary prophylaxis of CMV retinitis, though intraocular therapy alone does not protect contralateral eye or other organs and needs to be combined with systemic treatment. Frequent intravitreous injections are also impractical in most children. Intraocular implants should not be used in children <3 years of age due to small size of their eyes.

Secondary prophylaxis may be discontinued in adults or adolescents with CMV retinitis after sustained rise in CD4 counts >100 cells/mm^3 on antiretroviral therapy. Safety of discontinuing secondary prophylaxis following immune reconstitution in HIV infected children is not well established. However, based on experience in adult patients, discontinuing secondary prophylaxis may be considered in children who are: (a) on HAART, (b) have sustained rise in CD4 count for at least 6 months to >500 cells/mm^3 or >15 percent in children <6 yrs or >100 cells/mm^3 or >15 percent in children >6 yrs of age. Such decision should be made in close consultation with ophthalmologist considering anatomic location of the retinal lesion, vision in contralateral eye and feasibility of regular ophthalmologic monitoring. All patients in whom secondary prophylaxis has been discontinued should undergo regular ophthalmologic monitoring at 3-6 month intervals for early detection of CMV relapse or immune reconstitution uveitis.

Secondary prophylaxis should be reinstituted in children when CD4 count drops below the levels stated in criteria for discontinuation of prophylaxis.

Herpes Simplex Virus

Recurrent or persistent HSV infection is a common AIDS-indicator illness in HIV infected children. These children also have more prolonged shedding of virus after primary or reactivation HSV infection than those without HIV infection.

HSV infections are caused by two strains—HSV-1 that commonly infects skin and mucus membranes and HSV-2 that mainly infects genital tract. Neonatal HSV infections are usually HSV-2, acquired from an HSV-infected mother either as ascending *in utero* infection or more commonly as perinatal infection following contact with infected genital fluids during labor. Risk factors for neonatal HSV infection include: (a) Primary rather than reactivated HSV infection in mother, (b) Viral shedding in genital tract at the time of delivery, (c) Prolonged rupture of membranes and d) Invasive procedures during labor. HIV infected mothers have higher incidence of HSV infection as well as viral shedding in genital tract at the time of delivery. HSV coinfection in HIV infected mothers is also known to increase the risk of perinatal HIV transmission.

In childhood, HSV-1 infections are more common, usually acquired in early childhood as person-to-person transmission through direct contact with infected oral secretions or lesions. Infection rate increases with age and risk of transmission is higher in overcrowded living conditions, e.g. urban slums. Acquired HSV-2 infections are common in adolescents due to increased sexual activity.

Clinically, neonatal infection generally presents in second or third week of life with disseminated disease, localized CNS disease or superficial disease involving skin, eyes and mouth. Disseminated or neurological disease may present without skin lesions in ~40 percent cases, with higher-risk of neuro-sequelae than in cases with coexisting mucocutaneous disease.[33]

In non HIV population, orolabial herpes is the commonest manifestation of acquired HSV-1 infection, which usually subsides after 7-10 days even without treatment but may recur again, often triggered by sunlight or physiologic stress. Genital herpes is the more common manifestation of HSV-2 infection.

Immunocompromised HIV infected children, specially those with CD4 <100/mm^3 tend to develop more severe, prolonged and recurrent mucocutaneous disease or disseminated HSV involving CNS, esophagus, liver, lung, etc. HSV retinitis manifests as acute retinal necrosis and can lead to rapid loss of vision.

Diagnosis of superficial HSV lesions is easy, based on typical grouped distribution of vesicles. However, confirmation requires viral culture or DNA-PCR from superficial lesions, blood or body fluids, e.g. urine and stool. In newborns, positive cultures from any of these sites beyond 48 hours of birth indicate viral replication rather than contamination after intrapartum exposure. A Direct immunofluorescence test for HSV antigen may be used for rapid diagnosis on cells collected from skin, conjunctiva, or mucosal scrapings. Giemsa staining (Tzanck preparation) of lesion scrapings to show multinucleated giant cells and eosinophilic intranuclear inclusions is insensitive and nonspecific. Diagnosis of HSV encephalitis rests on CSF-PCR, as viral cultures are usually negative in CSF. Diagnosis of HSV esophagitis requires endoscopic biopsy and culture.

Exposure prevention: Since viral shedding in maternal genital secretions is most important source of infection for newborn, which is more common in HIV infected mothers, main strategies to reduce the risk of neonatal HSV infection involve: (a) Reduction of viral shedding by specific antiviral therapy in infected mother and (b) Reduction of baby's exposure to infected genital secretions by elective cesarean section. HAART regimens may decrease, but not prevent, the frequency of maternal genital HSV shedding and recurrence of genital lesions.

Antiviral therapy with acyclovir or valacyclovir near term in HIV-uninfected women with HSV infection reduces viral shedding and the need for cesarean delivery. However, efficacy of this strategy have not been evaluated in HIV/HSV coinfected women and is currently not recommended. There are reports of HSV infected neonates born to women who received anti-HSV therapy in last trimester.

Elective cesarean section, preferably prior to rupture of membranes is the most effective preventive strategy to prevent neonatal HSV infection in mothers with active genital HSV at the onset of labor.[34]

Prevention of postnatal HSV-1 exposure is difficult, though direct contact of HIV infected children with secretions from active HSV lesions of source, e.g. herpes labialis in mother or household members should be avoided.

In sexually active HIV infected adolescents, avoidance of contact with infected partners with herpes lesions and use of latex condoms during intercourse is advisable. However, sexual transmission can occur during asymptomatic shedding. Chronic suppressive therapy with valacyclovir in persons with genital herpes halves the risk of HSV-2 transmission to susceptible partners, though effectiveness of this strategy has not been evaluated in HIV-setting. HAART has been found to reduce the frequency of symptomatic herpetic lesions, but not the mucosal HSV-2 shedding.[35]

Primary prophylaxis: Following neonatal HSV infection, oral acyclovir therapy may prevent recurrence of skin disease but the effect on neurologic outcome needs further assessment. Till then, routine prophylactic therapy in newborns is not recommended. Antiviral prophylaxis to prevent initial episodes of HSV disease after exposure in older children is also not recommended.

Secondary prophylaxis: As episodes of HSV disease can be treated successfully, chronic therapy with acyclovir is not required after lesions resolve. However, children who have frequent or severe recurrences (>3 severe episodes in a year) can be administered suppressive therapy with acyclovir (PO 20 mg/kg/dose twice a day).[11] Valacyclovir or famciclovir (both PO 500 mg/dose twice a day) are other options for older children. Effective HAART therapy may also lessen the frequency of recurrence.

Varicella-Zoster Virus (VZV) Infections

Varicella-zoster virus (VZV) in HIV infected children is known to cause more severe disease at the time of primary infection (chicken pox) and higher frequency of severe, recurrent and multidermatomal disease during reactivation (herpes zoster) than in general population. HIV infected persons have 15-25 times higher-risk to develop zoster than non HIV persons.[36]

VZV is highly contagious, mainly transmitted from skin lesions of a case with secondary attack rates of ~80 percent in susceptible household contacts. Herpes zoster is less contagious than varicella.

As >85 percent pregnant women are already immune due to previous infection, mother-to-child transmission is rare. In case mother gets primary VZV infection during pregnancy, risk of transmission to newborn increases with gestation. Maternal VZV infection at the time of delivery carries an attack rate of 20-30 percent in newborns, lesser if mother has received specific antiviral therapy. It is unknown whether transmission risk is higher in HIV infected pregnant women with varicella. Few cases of congenital VZV have been reported, but none in HIV infected mothers.

Herpes zoster is common in HIV infected children, specially in those who had lower CD4 counts at the time of primary varicella infection. In HIV infected children with CD4 <15 percent at the time of primary varicella, the rate of subsequent zoster was ~70 percent. CD4 count also correlates with the frequency of zoster recurrences and the incidence of herpes zoster in HIV infected children is lesser in the HAART era than it was before it.

In adults, Herpes zoster can occur at any CD4+ count, but frequency is highest with CD4 counts <200 cells/mm^3 and is not reduced by ART.

Clinically, primary varicella disease is more severe, with longer course and higher rate of complications in HIV infected children, specially those who are not on HAART or have lower CD4 counts. Chronic persistent VZV with continued appearance of new lesions for >1 month after primary or recurrent infection has been reported in ~14 percent of HIV infected children with VZV.[37] The virus may become resistant to acyclovir during prolonged therapy.

HIV infected children have higher-risk of recurrent episodes of reactivated zoster infection with multi-dermatomal disease or even a disseminated rash similar to varicella. Encephalitis without rash has also been reported. Complications are more common in children with low CD4 counts and mainly include encephalitis, myelitis and retinitis, e.g. progressive outer retinal necrosis (PORN). Another variant of retinopathy, i.e. acute retinal necrosis (ARN) can occur at any, usually normal CD4 counts.

Diagnosis of varicella and herpes zoster can be easily made on clinical appearance, while atypical superficial lesions may need swab or biopsy for viral culture, immunofluorescent antigen testing or PCR. Histopathology and PCR also aid in diagnosis of visceral infections. PCR can differentiate between wild-type and vaccine VZV. Serology can be used to diagnose VZV infection, but it does not differentiate between primary and recurrent VZV infections.

Exposure prevention: Avoidance of exposure to persons with varicella or zoster disease is important for HIV infected children, who had no evidence of previous immunity (e.g. history of disease or vaccination), due to highly contagious nature of infection. Household contacts of these children without evidence of immunity should also receive varicella vaccine to prevent transmission of wild-VZV to HIV infected.

Primary prophylaxis against VZV involves specific immunization and postexposure prophylaxis. Varicella vaccine provides 80-85 percent protection in healthy children, though efficacy studies in HIV infected children are not available. All HIV infected children with CDC clinical categories N, A and B and CD4 counts ≥15 percent (or >200 in children >8 years) should receive two doses of varicella vaccine—first at the age of 12-15 months and the second after 3 months. Data regarding safety, immunogenicity, or efficacy of MMRV vaccine in HIV infected children is not available and it should not be used as a substitute for single-antigen varicella vaccine.[11]

Varicella vaccine is a live vaccine and HIV infected children with low CD4 levels (<15%) may develop pneumonia and neurologic manifestations following vaccination. These children should not be immunized against varicella. However, immunization of such children following immune reconstitution (CD4 ≥15%) with antiretroviral therapy can be considered. Herpes zoster following varicella vaccination has been reported in healthy children but not in HIV infected children.[38] If vaccination of HIV infected persons results in more severe clinical disease, acyclovir therapy might modify the severity of disease. VZV rashes <2 weeks after immunization, are usually due to wild-type VZV.

For postexposure prophylaxis, susceptible HIV infected children and adolescents without previous history of disease or vaccination should be passively immunized within 96 hours of exposure with varicella-zoster immune globulin (IM 125 IU/10 kg body wt, max 625 IU), though not easily available. In such cases, passive immunization with IVIG (IV 400 mg/kg single dose) may be considered as an alternative.

Another option for postexposure prophylaxis in susceptible HIV infected children is acyclovir prophylaxis (PO 80 mg/kg/d in four divided doses for 5-7 days, max 80 mg qid), if passive immunization is not possible or 96 hours have lapsed afer exposure. However, efficacy of postexposure prophylaxis with acyclovir is not established in susceptible HIV infected children and some expert advice to wait till the appearance of rash to start acyclovir therapy.

No preventive measures are available for zoster in HIV infected children. A vaccine for prevention of herpes zoster has been approved for use in immunocompetent adults >60 years of age. Data regarding safety and efficacy of this vaccine in HIV infected individuals of any age are lacking and its use in HIV infected individuals is presently not recommended.

Hepatitis B Virus (HBV) Infections

HBV is a common coinfection in HIV infected children, acquired vertically from infected mothers or horizontally via infected transfusions or sexual contacts. Risk of developing chronic hepatitis B infection is higher following perinatally-acquired infection (>90%) than when infection is acquired in later life. HIV/HBV coinfected persons are at higher-risk of developing cirrhosis, end-stage liver disease and liver-related mortality. Universal HBV vaccination has dramatically lowered rates of chronic HBV infection in children.

Clinically, majority of acute HBV infections in children are asymptomatic or present with mild hepatitis. Fuliminant hepatic failure and extrahepatic manifestations are uncommon. Most children with chronic HBV infection are also asymptomatic, but may develop cirrhosis or hepatocellular carcinoma in 25 percent cases after two to three decades.

Diagnosis rests on serology and various serological markers appear and disappear during the natural history of disease with different significance. HIV-HBV coinfected children have higher frequency of isolated high anti-HBc titers (suggestive of chronic HBV infection) and higher HBV-DNA levels (suggestive of progressive liver disease).

Exposure prevention: All pregnant women, including HIV infected women, should be tested for HBsAg during an early prenatal visit in each pregnancy and testing should be repeated in late pregnancy for HBsAg-negative women at high-risk for HBV infection. Pregnancy is not a contraindication to HBV vaccination in previously unimmunized women as current vaccines contain noninfectious HBsAg with no risk to the fetus.

HIV infected children and their caretakers should be counseled about need for HBV vaccination and avoidance of high-risk behavior, e.g. intravenous drug abuse, body tattooing, sharing of toothbrushes or other personal care articles and unsafe sexual exposure.

Primary prophylaxis: All infants born to HBV infected women, including HIV-coinfected women, should receive Hepatitis B immunoglobulin (HBIG) and HBV vaccine within 12 hours of birth, followed by two more doses of vaccine at 1 and 6 months of age (0, 1, 6 month schedule). In preterms <2 kg, at-birth dose should not be counted due to potentially reduced immunogenicity of vaccine in them and an additional dose should be administered at 2 months (0, 1, 2, 6 month schedule). Later, all infants born to HBsAg-positive women should be tested for anti-HBs antibodies and HBsAg at 9-18 months of age and those who are HBsAg negative and have anti-HBs levels <10 mIU/mL should be revaccinated with a second three-dose series (0, 1, 2 month schedule).[39]

Three-dose series (0, 1, 6 months) of HBV vaccine is recommended for all children and adolescents aged <19 years including HIV infected children. Some specialists recommend that HIV infected persons with anti-HBc alone should be tested for HBV DNA before vaccination for HBV or before initiating ART due to the risk for reactivation of HBV and the occurrence of IRIS.

Diminished antibody responses may be seen in HIV infected children, especially in older ones or those with CD4 counts <200 cells/mm^3.[3,39] For this reason, HIV infected infants, children and adolescents should be tested for anti-HBs antibodies after 1-2 months of last dose in vaccination series and if levels are <10 mIU/mL, revaccinated with a second three-dose series of HBV vaccine. Modified HBV vaccine dosing regimens, including double-strength antigen dose, might increase response rates. The need for booster doses of HBV vaccine in HIV infected persons has not been determined. Annual anti-HBs antibody testing and booster doses when these levels drop <10 mIU/mL should be considered in persons with ongoing risk of HBV exposure.[40]

Hepatitis C Virus (HCV) Infections

HCV infections are more common in HIV infected children than in non HIV children. Perinatal transmission is the predominant mode of HCV acquisition in children, followed by blood product transfusions, needlestick injuries and sexual exposure in older childen. Risk for perinatal HCV transmission is higher in mothers with HIV/HCV coinfection than in mothers with isolate HCV infection. Dual-virus transmission has been reported in 4-10 percent of children born to HIV/HCV coinfected mothers.

Clinically, children with perinatal HCV infection usually have more benign course than adults with acquired HCV infection. In HIV/HCV coinfected adults, the natural history of HCV infection appears to be accelerated, with more rapid progression to cirrhosis, decompensated liver disease, malignancy and death. However, data on the effect of HIV/HCV dual infection on the natural history of HCV or HIV infection in children is insufficient.

Diagnosis rests on serology and nucleic acid tests. Since serological tests may be positive in children <18 months due to passively transferred antibodies from mother, HCV infection can be diagnosed in infancy only by nucleic acid tests for the detection of HCV RNA. Due to intermittent viremia, a single negative HCV RNA test is not conclusive and should be tested on at least two occasions between the ages of 2 and 6 months to exclude HCV infection.

A positive anti-HCV antibody test in a child >18 months of age is indicative of HCV infection. A positive HCV-RNA test confirms the presence of HCV infection and, if positive for >6 months, suggests the presence of chronic infection. Liver biopsy is required to assess severity of hepatic disease and to decide the need to initiate therapy for chronic HCV infection.

Exposure prevention: All HIV infected pregnant women should be screened for HCV and appropriate antiretroviral therapy in them may reduce the risk of perinatal HCV transmission. No other measures are reliable to prevent perinatal HCV transmission. Cesarean delivery and avoidance of breastfeeding, known to reduce perinatal HIV transmission are not associated with reduced risk of perinatal HCV transmission.

Avoidance of other risk-factors, e.g. untested blood transfusions, needlestick injuries and unprotected sex are other measures to reduce exposure to HCV infection. Currently no vaccine is available to prevent HCV infection.

Primary prophylaxis: All HIV infected children should be screened for active HCV infection and those with HIV/HCV-coinfection should be offered antiviral treatment to prevent development of HCV-related liver disease complications. These children should also be immunized against HBV and HAV infection, as these infections are often more fulminant in presence of underlying HCV hepatitis. In coinfected persons with cirrhosis, measures to identify and prevent complications of advanced liver disease are identical to those established in persons without HIV.

Toxoplasmosis

CNS toxoplasmosis is rare in HIV infected children than in infected adults, reported in <1 percent AIDS cases during Pre-HAART era and 0.2 percent cases on HAART.[10]

Toxoplasma gondii infection in young children is acquired *in utero* from infected mothers, while older children may acquire it by consuming undercooked meat containing tissue cysts or ingestion of food and water contaminated with sporulated oocysts. Person to person transmission is unknown.

Perinatal transmission occurs almost exclusively when mother is infected *during pregnancy* and risk for transmission increases with the gestation at the time of maternal infection. Prenatal transmission from mothers with chronic toxoplasma infection acquired before pregnancy is extremely rare in seronegative mothers but may occur in <4 percent newborns of HIV-positive mothers presumably due to reactivation of parasitic replication in women with severe immunosuppression.[41]

Clinically, congenital toxoplasmosis is asymptomatic in ~70-90 percent newborns at birth, but majority of them develop late ophthalmic or neurological complications after many months or years. In immunocompetent hosts, acquired toxoplasmosis is often asymptomatic, but some cases may present with nonspecific mononucleosis-like syndrome.

In HIV infected children, clinical disease is rare with CD4+ counts >200 cells/mm^3 with greatest risk at CD4 count <50 cells/mm^3, usually representing reactivation of latent tissue cysts. *Focal encephalitis* is the commonest

presentation of toxoplasmosis with multiple contrast-enhancing lesions on neuroimaging. Ocular toxoplasmosis is another important presentation with/without visual loss. However, isolated ocular toxoplasmosis is rare, usually seen with CNS infection. Uncommon presentations include pneumonitis, hepatitis and myocarditis.

Diagnosis of congenital toxoplasmosis rests on detection of *Toxoplasma*-specific IgM, IgA, or IgE antibodies within first 6 months of life or persistence of specific IgG antibody beyond 12 months of age. Isolation of the parasite in tissue cultures or detection of *Toxoplasma* DNA by PCR in body fluids is highly specific but with poor sensitivity. DNA-PCR is usually negative if therapy has been started. Presumptive diagnosis of CNS toxoplasmosis rests on clinical symptoms, serologic evidence of infection and presence of a space-occupying lesion on neuroimaging, while definitive diagnosis requires stereotactic CT-guided brain biopsy, reserved for nonresponders.

Exposure prevention: HIV infected women are at higher-risk to transmit infection to their fetuses and serologic testing for *Toxoplasma* should be performed in all HIV infected pregnant women. All infants, whose mothers are HIV infected as well as seropositive for *Toxoplasma* should be evaluated for congenital toxoplasmosis. However, routine *Toxoplasma s*creening of perinatally HIV infected children whose mothers do not have toxoplasmosis is generally not recommended due to low prevalence of disease.

All HIV infected children should be counseled to: (a) avoid consuming raw/undercooked meat, (b) wash hands after contact with raw meat/soil, (c) wash fruits/vegetables before eating and d) avoid contact with stray cats.

HIV infected older children and adolescents should be tested for IgG antibody to *Toxoplasma* soon after the diagnosis of HIV infection to detect latent infection with *T. gondii*.

Primary prophylaxis is recommended to all *Toxoplasma*-seropositive children with severe immunosuppression, though critical levels of immunosuppression are not well-defined in children. In general, children >6 years should receive prophylaxis at CD4 count <100 cells/mm^3 while younger ones might be started on prophylaxis earlier at CD4 count <15 percent.[11,12]

Cotrimoxazole or TMP-SMX (PO 150/750mg/m^2 daily in two divided doses) is the preferred drug for *Toxoplasma* prophylaxis, also effective against PCP. In patients who cannot tolerate TMP-SMX, recommended alternatives are dapsone-pyrimethamine (also effective against PCP) or atovaquone with/out pyrimethamine. Single-drug prophylaxis with dapsone, pyrimethamine, azithromycin, or clarithromycin is not recommended on the basis of available data, while aerosolized pentamidine does not protect against *Toxoplasma* encephalitis.

Toxoplasma-seronegative children who are not on PCP-prophylaxis regimens active against *Toxoplasma* should be retested for *Toxoplasma*-IgG when CD4 count declines <100 cells/mm^3 to determine whether they have sero-converted and need *Toxoplasma* prophylaxis.

Prophylaxis against *Toxoplasmosis* should be discontinued in HIV infected adolescents who have responded to HAART with sustained rise in CD4 count >200 cells/mm^3 for >3 months.[12] There are no data on the safety of discontinuing primary *Toxoplasma* prophylaxis in HIV infected under-five children, but based on adult data, it might be safe to discontinue it once a child responds to HAART with sustained rise in CD4 counts >15 percent for >3 months. For children >6 years, same CD4 count as for HIV infected adolescents can be used. Prophylaxis should be reintroduced if CD4 count drops <100–200 cells/mm^3 (in adolescents) or <15 percent (in children).

Secondary prophylaxis is indicated in all patients who have completed initial therapy for acquired *Toxoplasma* encephalitis unless there is immune reconstitution with antiretroviral therapy.[11] The combination of pyrimethamine (PO 1 mg/kg/day) plus sulfadiazine (PO 85-120 mg/day in 2-4 divided doses) with leucovorin (PO 5 mg/every 3 days) is highly effective for this purpose and also provides protection against PCP. A commonly used regimen for patients who cannot tolerate sulfa drugs is pyrimethamine plus clindamycin, though this regimen does not protect against PCP. Based on adult data, atovaquone with or without pyrimethamine also can be considered in children for this purpose, which is also active against PCP but more expensive. Limited data support the use of TMP-SMX for secondary prophylaxis, which should only be used in children intolerant to pyrimethamine-sulfadiazine or pyrimethamine-clindamycin combinations.

Safety of the discontinuation of secondary prophylaxis after immune reconstitution with HAART in children has not been studied extensively. Adolescents on secondary prophylaxis are at low-risk for recurrence of toxoplasma encephalitis if they have successfully completed their initial therapy, remain asymptomatic and have sustained rise CD4 count >200 cells/mm^3 for >6 months on HAART therapy.[12] In view of adult data, discontinuation of secondary *Toxoplasma* prophylaxis may be considered in HIV infected children <6 years of age after they have: (a) completed *Toxoplasma* encephalitis therapy, (b) remained asymptomatic and c) achieved CD4 counts >15 percent for >6 months on HAART.[11] For children >6 years, the same criteria as for adolescents can also be used.

Highest risk for relapse for *Toxoplasma* encephalitis is within first 6 months of stopping secondary prophylaxis and some specialists recommend MRI to determine whether brain lesions had resolved before stopping secondary prophylaxis. Secondary prophylaxis should be reintroduced if the CD4+ count drops <200 cells/mm^3 at any time.

Malaria

Malaria and HIV, both are common in developing countries and cause substantial morbidity and mortality. Given this overlap, even modest interactions between them have public health importance.

HIV disease impairs the acquired immunity to malaria and recent data suggest increased frequency of clinical malaria, higher density of parasitemia and increased risk of severe anemia and hospitalization in HIV infected children compared with those without HIV.

On the other hand, malarial episodes are associated with increased HIV viral load. Recent studies have confirmed that malaria parasitemia was associated with increased HIV concentrations in pregnant women and consequently, higher-risk of perinatal HIV transmission to baby. Placental infection during malarial episode in pregnant mother has also been associated with increased expression of CCR5 receptors in placental macrophages, increasing risk of perinatal HIV transmission.

Clinical presentation of malaria in HIV infected children is generally similar to that in other children. However, HIV infected infants are more likely to have severe or complicated malaria.[42] Unlike adults, studies in young children in malaria-endemic areas have not found an increased frequency or density of parasitemia with HIV infection, except few exceptions.

Diagnosis of malaria rests on microscopic examination of peripheral blood smear. Rapid diagnostic tests based on antigen detection or monoclonal antibodies to parasitic products offer specificity of ~ 100 percent and sensitivity of 85-95 percent.

Exposure prevention: All mosquito-bite preventive measures for general population also apply to HIV infected children, including personal protective measures.

Primary prophylaxis with antimalarial drugs is impractical in children living in malaria endemic regions, but should be advised to those who are traveling to endemic regions for short periods. Recommendations for chemoprophylaxis are the same for HIV infected as for non HIV persons, using mefloquine, doxycycline or atovaquone-proguanil. However, chemoprophylaxis is not 100 percent effective. In nonholoendemic areas, there is some protection with TMP-SMX prophylaxis in combination with the use of bed nets, resulting in >90 percent reduction in clinical malaria in one study.[43] However, TMP-SMX is not recommended as an antimalarial prophylactic regimen.

Secondary prophylaxis: With the exception of reactivation of *P. vivax* and *P. ovale* hypnozoites, malaria, once successfully treated, does not recur. Malaria infection does not infer protective immunity and continued exposure to malaria parasites can result in repeated infection.

Leishmaniasis

HIV leishmaniasis coinfection is an important but rarely reported problem in Asia and Africa, caused by various species of *Leishmania* genus—obligate intracellular protozoa that survive and replicate in intracellular vacuoles within macrophages. Most infections in immunocompetent hosts are asymptomatic. However, *Leishmania* remain viable in healthy persons for long periods, leading to a susceptible population if immunosuppression occurs.

Clinically, *Leishmania* manifestations in HIV infected children without severe immunosuppression are similar to those in non HIV population. Splenomegaly is less common in HIV coinfected patients. Disease tends to be more severe in those with advanced immunosuppression (CD4 <200 cells/mm^3) and relapses are common. In these cases, atypical presentations, e.g. esophagitis are also common.

Diagnosis rests on demonstration of characteristic amastigote forms (LD bodies) in blood, bone marrow, splenic aspirate or other tissue specimens on smear or culture. Serological tests to detect antibodies against *Leishmania* antigens are substantially less sensitive in HIV coinfected patients. A PCR test to demonstrate *Leishmania* in the blood or tissue of coinfected patients has >95 percent sensitivity. Leishmanial skin tests are nearly always negative in active visceral leishmaniasis, with or without HIV coinfection.

Exposure prevention involves early diagnosis and treatment of reservoirs, vector-control activities and personal protection measures, e.g. use of insecticide-treated nets.

Primary prophylaxis is not possible and currently no vaccine is available.

Secondary prophylaxis: Relapses are common following cessation of therapy for visceral leishmaniasis in immunosuppressed patients with AIDS. In cases who are not on HAART, the risk of relapse at 6 and 12 months in the absence of secondary prophylaxis is 60 and 90 percent, respectively.[44] Therefore, secondary prophylaxis with an effective antileishmanial drug is recommended, specially in cases of visceral leishmaniasis with CD4 counts <200 cells/mm^3.[3,12] Existing data are insufficient to recommend a specific regimen. Prophylaxis with ABLC,

pentavalent antimony or lipid formulations of amphotericin, given at 2-4 weeks interval was also associated with decreased relapse rates. Daily allopurinol prophylaxis is less effective and not recommended. Although, data are insufficient, discontinuation of secondary prophylaxis after successful treatment of leishmaniasis might be considered after a sustained (>3-6 months) rise in CD4 count >350 cells/mm^3 after initiation of ART.[12]

Cryptosporidiosis, Microsporidiosis and Isosporiasis

Many species of these spore-forming protozoa—*Cryptosporidium* (sp. *C. parvum),* Microsporidia (sp. *Enterocytozoon bieneusi, Encephalitozoon intestinalis)* and *Isospora (I. belli)* are known to cause moderate to severe diarrhea, specially in HIV infected population. However, small outbreaks with milder illness are not uncommon in non-HIV children and elderly people. Infection is acquired by fecal-oral route due to ingestion of food or water contaminated with oocysts. Incidence of both infections has declined dramatically in HAART era, though they continue to be an important cause of chronic persistent diarrhea in HIV infected children of developing countries with poor antiretroviral coverage.

Clinically, nonbloody, watery, persistent diarrhea is the most common manifestation of these infections in HIV infected children, which tends to be more severe and persistent in cases with advanced immunosuppresion often leading to failure to thrive, fluid and electrolyte imbalance and occasionally death. Clinically, these infections cannot be differentiated with each other or with other causes of diarrhea in children.

Extraintestinal manifestations are more common in HIV infected children with prolonged disease and low CD4 counts. *Cryptosporidium* can migrate to bile duct causing acalculous cholecystitis, sclerosing cholangitis and pancreatitis, specially in HIV infected cases with prolonged disease and low CD4+ counts. Rarely, pulmonary or disseminated disease can occur in immunocompromised children. Nondiarrhreal manifestations of microsporidia infections depend on the causative species, including hepatitis, peritonitis, keratoconjunctivitis, myositis, cholangitis, respiratory disease, sinusitis, encephalitis and disseminated disease. Acalculous cholecystitis and reactive arthritis has been reported after *Isospora* infections.

Diagnosis usually rests on stool microscopy after special staining and most of these pathogens cannot be cultivated in culture. Oocysts might be shed intermittently and stool examination may be negative in cases with low parasite load. Antigen-detection assays are available with good sensitivity and excellent specificity. Endoscopic small bowel biopsy should be considered in all patients with chronic diarrhea of >2 months duration and negative stool examinations. PCR amplification of parasite DNA sequences in stool or biopsy specimens is highly sensitive but not easily available. Molecular methods, e.g PCR hold promise to further enhance sensitivity. Urine sediment examination by light microscopy may be used to detect microsporidia spores in disseminated disease.

Exposure prevention: Avoidance of contact with contaminated water or food, not only by patients but also by their caretakers, is the most important means to reduce protozoal load in community and disease in children. Consumption of only safe-potable water, preferably after boiling is important, as chlorination of public water supply may be inadequate to eliminate spore-forming protozoa. Handwashing after exposure to potentially contaminated material and minimized exposure to sick pets are also important preventive measures against exposure to these pathogens. *Cryptosporidium*-infected patients should not work as food handlers.

In hospital, standard precautions, e.g. frequent hand washing is sufficient to prevent transmission of cryptosporidiosis from an infected patient to a susceptible HIV infected person, though some experts recommend that severely immunocompromised HIV infected patients should not share a room with a patient with cryptosporidiosis due to risk of transmission via fomites.

Primary prophylaxis: Since these infections are more frequent and more severe in HIV infected individuals with advanced immunodeficiency, effective antiretroviral therapy to prevent or restore immune status is the primary mode of prevention in HIV infected children.

Some studies suggested that rifabutin or clarithromycin prophylaxis for MAC may be associated with decreased rates of cryptosporidiosis.[45,46] However, the data are conflicting and insufficient to recommend these drugs solely for prophylaxis of cryptosporidiosis. No prophylactic regimens are known to prevent microsporidiosis. Although TMP-SMX prophylaxis for PCP has been associated with a lower frequency of isosporiasis, data are insufficient to recommend it use for primary prophylaxis of isosporiasis.

Secondary prophylaxis is not known to prevent recurrence of cryptosporidiosis or microsporidiosis. However, treatment for ocular microsporidiosis should be continued indefinitely as recurrence or relapse might follow treatment discontinuation.

Chronic maintenance therapy with TMP-SMX is recommended in HIV infected adults with CD4 counts <200 cells/mm^3,[12] which can be discontinued in cases with no evidence of active *I. belli* infection and sustained

rise in CD4 counts above these levels after antiretroviral therapy for at least 6 months. Other alternatives include pyrimethamine or ciprofloxacin. No recommendations are available for children.

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5.5

Risks and Management of Occupational and Nonoccupational Exposure in Pediatric HIV

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Introduction

Primary prevention, i.e. preventing exposure to Human Immunodeficiency Virus (HIV) is by far the most effective mechanism of preventing infection in community as well as in occupational settings. However, when exposure does occur, administration of antiretroviral agents for secondary prevention may be required.[1] Although there have been significant advances in our knowledge on management of occupational exposures, many issues relating to post exposure prophylaxis still remain unresolved. This chapter reviews the current understanding of different aspects of occupation exposure to HIV, its epidemiology, pathogenesis and management.

Administration of antiretroviral agents to prevent HIV infection after an exposure has already occurred is termed as post exposure prophylaxis while the administration of antiretroviral agents before the exposure is termed as pre-exposure prophylaxis.

Recent studies on pre-exposure prophylaxis have added another dimension to the management of exposure and prevention of HIV. Nonoccupational Pre exposure prophylaxis (nEP) is an approach to HIV prevention in which antiretroviral agents are used by an individual prior to or within 72 hours of potential HIV exposure to reduce the likelihood of infection. nEP should be distinguished from Post exposure Prophylaxis (PEP) in which an individual takes antiretroviral drugs soon after a potential exposure with the goal of reducing the likelihood of infection.[2]

HIV post exposure prophylaxis (PEP) is a form of secondary HIV prevention that is used to reduce the risk of HIV transmission when a health care worker is exposed to HIV during his work. PEP it has been shown to reduce risk of transmission rate by 81percent.[3] Although preventing exposures to blood and body fluids is the primary means of preventing occupationally acquired Human Immunodeficiency Virus (HIV) infection, appropriate post exposure management is an important element of workplace safety.

In 1996, the first US Public Health Service (PHS) recommendations for the use of post exposure prophylaxis (PEP) after occupational exposure to HIV were published; these recommendations have been updated twice[3]. Since publication of the most recent guidelines in 2001, new antiretroviral agents have been approved by the Food and Drug Administration (FDA), and additional information has become available regarding the use and safety of HIV PEP. In India, National AIDS Control Organization issued updated guidelines for the country for PEP prophylaxis in January 2009.[4]

Post Exposure Prophylaxis Following Occupational Exposure to HIV

Health Care Personnel (HCP) are normally at a very low risk of acquiring HIV infection during management of an HIV infected patient. However, the absence of a vaccine or effective-curative treatment following an accidental occupational exposure makes the health care personnel apprehensive. So, it is very necessary for all institutions to have a comprehensive program in place to deal with any accidental exposure to blood or body fluids of an HIV infected person.

Some of the vital issues dealing with transmission of HIV to HCP are:

- Who is at risk?
- How much is the risk?
- What factors influence this risk?
- How to reduce the risk?
- What is the role of antiretroviral agents in reducing this risk?
- Issues about safety of PEP drugs and their use in pregnancy
- Need to develop a comprehensive program for PEP implementation.

Who is at Risk?

All categories of Health Care Personnel (HCP) are at a potential risk of acquiring HIV infection during care of an HIV infected patient. Needle stick injuries in health care practice are inevitable. Majority of the injures were reported in resident doctors and surgeons. The commonest work place of injury were critical care unit and operation theaters[5,6]

Health Care Personnel and Exposure

Health Care Personnel (HCP) are defined as persons (e.g. hospital employees, medical and nursing students, clinicians, public safety workers or volunteers) whose activities involve contact with patients or with blood or other body fluids from patients in a health care or laboratory setting.

An "exposure" that may place an HCP at risk of HIV infection is defined as a percutaneous injury (e.g. needle-stick or cut with a sharp instrument), contact of mucous membrane or non-intact skin (particularly when the exposed skin is chapped, abraded, or afflicted with dermatitis), or contact with intact skin when the duration of contact is prolonged (e.g. several minutes or more) with blood or other potentially infectious body fluids. Body fluids that are potentially infectious include – blood, semen, vaginal secretions, cerebrospinal fluid, synovial, pleural, peritoneal, pericardial and amniotic fluids or other body fluids contaminated with visible blood. Exposure to tears, sweat, urine, faeces, saliva of an HIV infected person is normally not considered as an "exposure" unless these secretions contain visible blood.

Professionals with Frequent Blood Exposures

- Surgeons
- Emergency care providers
- Dentists
- Nurses
- Labor and delivery room personnel
- Laboratory technicians

What is the Average Risk of Acquiring HIV Infection After an Occupational Exposure?

The risk is normally very low, but it is not zero. The average risk of acquiring HIV infection after different types of occupational exposure is given in Table 5.5.1.[7]

As is evident, the average risk of acquiring HIV infection after a needle stick injury is 0.3 percent, while the comparable risk for HBV and HCV is 9 to 30 percent and 1 to 10 percent, respectively.

How Many Health Care Personnel have been Infected Occupationally?

As on June 2000, in USA, there were 56 reported cases of HCP with documented HIV seroconversion associated with an occupational exposure (Table 5.5.2). Another 138 cases are considered due to possible occupational exposure as these had history of occupational exposure, and no other risk factors for HIV but seroconversion was not documented. However, as per reported data globally, there are 98 confirmed and 194 possible cases of HCP infected occupationally. In India, there is only one documented case reported to NACO of a HCP acquiring HIV due to occupational exposure.

What Factors Influence this Risk?

Various epidemiological and laboratory studies have shown that the risk of infection varies with type of exposure factors such as:

- Type of needle (hollow bore vs. solid)
- Device visibly contaminated with patient's blood
- Depth of injury
- The amount of blood involved in the exposure
- The amount of virus in patient's blood at the time of exposure
- Whether PEP was taken within the recommended time

How to Reduce this Risk?

Before discussing the post-exposure prophylaxis, it must be emphasised that prevention remains the mainstay and universal precautions must be followed by all health care workers at all the times. Also all the patients must be seen as potentially infectious because it may not be practical or desirable to test all the patients for HIV. The standard (universal) precautions are well known to the medical personnel but they are not followed in usual practice, may be due to lack of facilities particularly in

Table.5.5.1: Occupational exposure

Average risk of HIV infection after an occupational exposure	
Small amount of blood on intact skin	No risk
Risk with damaged skin/prolonged exposure	1 in 1000
Exposure on eyes, nose or mouth	1 in 1000
Needle Stick/other sharp injuries	1 in 300

(Risk from all "exposures" increases further if exposure involves a large volume of blood or a higher amount of HIV in patients's blood as in patients with acute HIV infection or AIDS patient near death.)

Table 5.5.2: HCP exposure

Type of exposure of 55 documented cases		*Type of fluid involved in exposure*	
Needle stick/cuts/sharp injuries	48	Blood	50
Eye, Nose, Mouth, Skin exposure	5	Concentrated virus in lab.	3
Both injury and mucous membrane exposure	1	Visibly body fluid	1
Unknown	1	Unspecified fluid	1

district hospitals and primary health centers. But sometimes even when the facilities are available, there is a certain degree of complacency among doctors and other health care workers. This complacency has to be removed and concept of universal precautions has to be put to actual use once again in this era of emerging and re-emerging infections. One must remember that "Prevention is the mainstay of strategy to avoid occupational exposure to HIV".

Protective Barriers

Whenever exposure to blood/other potentially infected fluids is anticipated, protective barriers must be used.

a. ***Latex or vinyl gloves*** must be worn while carrying out any procedure and be decontaminated after each use. Gloves with holes/tears should not be used. Double gloves are not preferred as these are not more protective than single glove and this may be more clumsy also. Heavy-duty rubber gloves should be used for cleaning instruments, handling soiled linen or spills of blood/body fluids. These can be washed and reused.

b. ***Gowns and aprons*** protect one from splashes of blood or body fluids, e.g. during surgery/delivery. One may wear a waterproof gown or a sterile cloth with a plastic apron underneath. Protective eyewear (swimming goggles) may be used to prevent transmission by splash of fluids to the mucous membrane.

Safe Handling of Sharps

- Careful handling of hollow bore needle is very essential as it may lead to deep injuries.
- The needles should never be recapped. In situations where recapping is essential, single hand method should be used.
- Needles should never be bent/broken by hand.
- Needles should not be left on trolleys and beds and must be disposed off immediately.
- Never pass used sharps from one person to another directly.
- Use forceps instead of fingers for guiding sutures.
- The sharps should be disposed off in a puncture resistant container containing bleach.

What should be Done on Exposure to HIV Infected Blood/Body fluids?

Immediately following an exposure:

- Needle stick injuries and cuts should be washed with soap and water;
- Pricked finger should not be put into mouth reflexly;
- Splashes to the nose, mouth or skin, should be flushed with plenty of water;
- Eyes should be irrigated with clean water, saline, or sterile irrigants;

No scientific evidence exists as to the fact that the use of antiseptics for wound care or squeezing the wound will reduce the risk of transmission of HIV. However, use of antiseptics is not contraindicated. The use of a caustic agent such as bleach is not recommended.

One must report an "exposure" immediately to the appropriate authorities and condition must be treated as an emergency. Prompt reporting is essential because in some cases, HIV-PEP may be recommended and it should be started as soon as possible, preferably within a few hours. Initiating treatment after 72 hours of exposure is usually not recommended.

Is there Some Treatment Available After an Occupational Exposure to HIV?

Post exposure prophylaxis began in the early 1990 in an effort to protect the health care workers from HIV. The Centers for Disease control and Prevention (CDC) case control database on the use of Zidovudine as PEP provides the only available data for PEP. These suggest an 81 percent reduction in the likely hood of HIV transmission in health care workers who have administered monotherapy after occupational exposure. It has also been shown that delaying initiation, shortening the duration or decreasing the antiretroviral dose of PEP, individually or in combination, decreased its prophylactic efficacy.[8]

However, little information exists about efficacy of PEP in humans as seroconversion is infrequent following an occupational exposure to HIV infected blood; it would need thousands of HCP to enroll in a prospective study to achieve the statistically significant results on efficacy of PEP.

Also the experience in HIV infected patients has shown that combination of different antiretroviral agents is superior to monotherapy regimen, so a combination of two or three drugs in PEP regimen should be more beneficial than a single drug. One needs to consider toxicity of a combination regimen vis-à-vis risk of transmission.

NRTI combinations being considered for PEP include ZDV and 3TC, 3TC and d4T, and ddI and d4T. In previous regimens ZDV and 3TC were considered as first regimen but emergent resistance to ZDV and 3TC in certain geographical areas may demand different initial combinations.

The addition of a third drug for PEP in high risk exposures is based on their demonstrated effectiveness in reducing viral burden in HIV infected persons. Previously indinavir or nelfinavir were recommended as first choice agents in "Expanded PEP Regimens". But now with chances of PI resistance particularly on exposure to blood/blood fluid of patients who are already on triple therapy, efavirانz (EFV) and Abacavir (ABC) are being considered as alternatives. Nevirapine has not been

recommended for use in PEP regimen due to reports of fatal hepatic complications in some cases.

Failure of PEP to prevent HIV infection in HCP has been reported in at least 21 cases (16 on ZDV, two on ZDV and ddI and three on triple drug combination).

How PEP Works?

PEP is recommended (Table 5.5.3) because it has been observed that systemic infection does not occur immediately after an exposure and there is a brief window period of opportunity available to contain or eradicate HIV from body before wide spread cellular infection occurs.

After a needle-stick injury, immune cells (dendritic) in skin present the HIV to T-lymphocytes and natural killer cells. It is seen that in monkey models, SIV when injected into vagina, virus is engulfed by immune cells in the vaginal lining. Within 2 days SIV is found in inguinal lymph nodes. Within 5 days SIV infected T cells and free SIV can be detected in blood stream. Migration of SIV after rectal or penile tip exposure follows a similar time frame. PEP can stop viral replication during this early period before it gains a 'foothold' in the body.

Is Postexposure Prophylaxis Recommended for all Types of Occupational Exposures to HIV?

Not so, because most occupational exposures do not lead to HIV infection. The chances of possible serious side effects (toxicity) from the drugs used for PEP may be much greater than the chance of HIV infection from such exposures. Both risk of infection and possible side effects of drugs should be carefully considered when deciding whether to give postexposure prophylaxis or not.

Table 5.5.3: Determine the PEP recommendation

EC	*HIV SC*	*PEP recommendation*
1	1	PEP may not be warranted
1	2	Consider **basic regimen** (Exposure type poses a negligible risk for HIV transmission).
2	1	Recommend **basic regimen** (Most HIV exposures are in this category; no increased risk for HIV transmission has been observed but use of PEP is appropriate).
2	2	Recommend **expanded regimen** (Exposure type represents an increased HIV transmission risk.)
3	1 or 2	Recommend **expanded regimen** (Exposure type represents an increased HIV transmission risk.)
Unknown		When unknown, if the source, (in the case of an unknown source), the setting where the exposure occurred, suggests a possible risk for HIV exposure and the EC is 2 or 3, consider PEP basic regimen.

The decision to start PEP is made on the basis of extent and severity of exposure to HIV (Exposure Code) and the HIV status of the source (HIV Status Code) with whose blood/body fluids the exposure has occurred. The Exposure Code and HIV Status Code (Flow chart 5.5.1) are then collated to arrive at a decision regarding initiation of PEP.

Determination of the Exposure Code (EC)

Exposure code can be defined as per the (Flow Chart 5.5.2) given. It may be classified into three categories, EC-1, EC-2 and EC-3, depending upon the severity of exposure.

What Specific Drugs are Recommended for PEP?

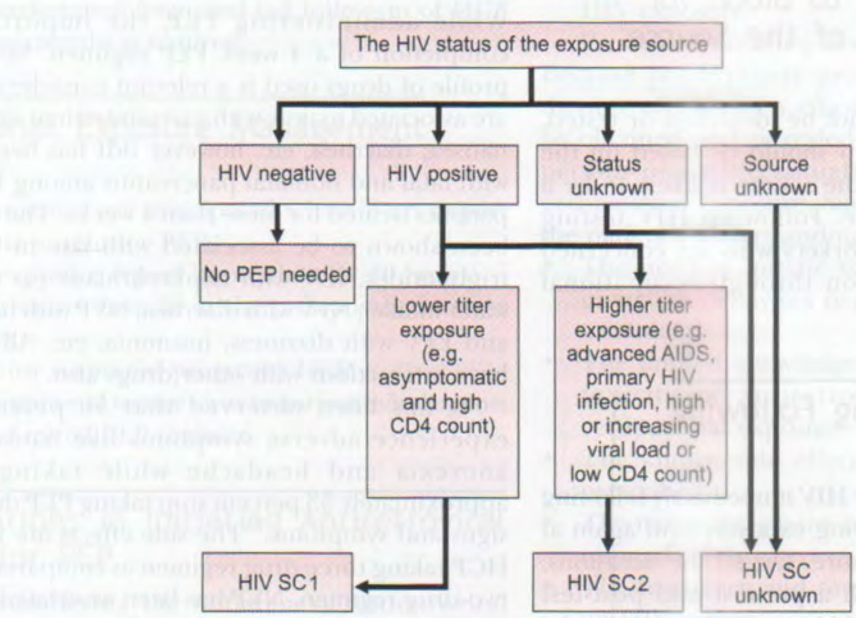
These are the guidelines recommended at present by National AIDS Control Organization, Government of India. However, with the use of antiretroviral therapy for HIV infected patients, the issue of transmission of drug resistant virus (particularly in the developed world where large numbers of infected persons are on triple therapy) is emerging as a serious consideration in choosing drugs for PEP. Detailed guidelines in this regard can be accessed from updated USPHS guidelines issued in June 2001[3] and NACO guidelines in January 2009[4]

Basic Regimen: (4 weeks therapy)	Zidovudine (AZT/ZDV) - 300 mg twice a day is used for all types of exposure + Lamivudine (3TC) - 150 mg twice a day is added to increase the effectiveness of ZDV and to prevent resistance to ZDV
Expanded Regimen: (4 weeks therapy)	Basic Regimen (AZT/ZDV + 3TC) + Indinavir - 800 mg/thrice a day or any other protease inhibitor is added for higher risk categories. Presently EFV is also used for PEP in place of PI.

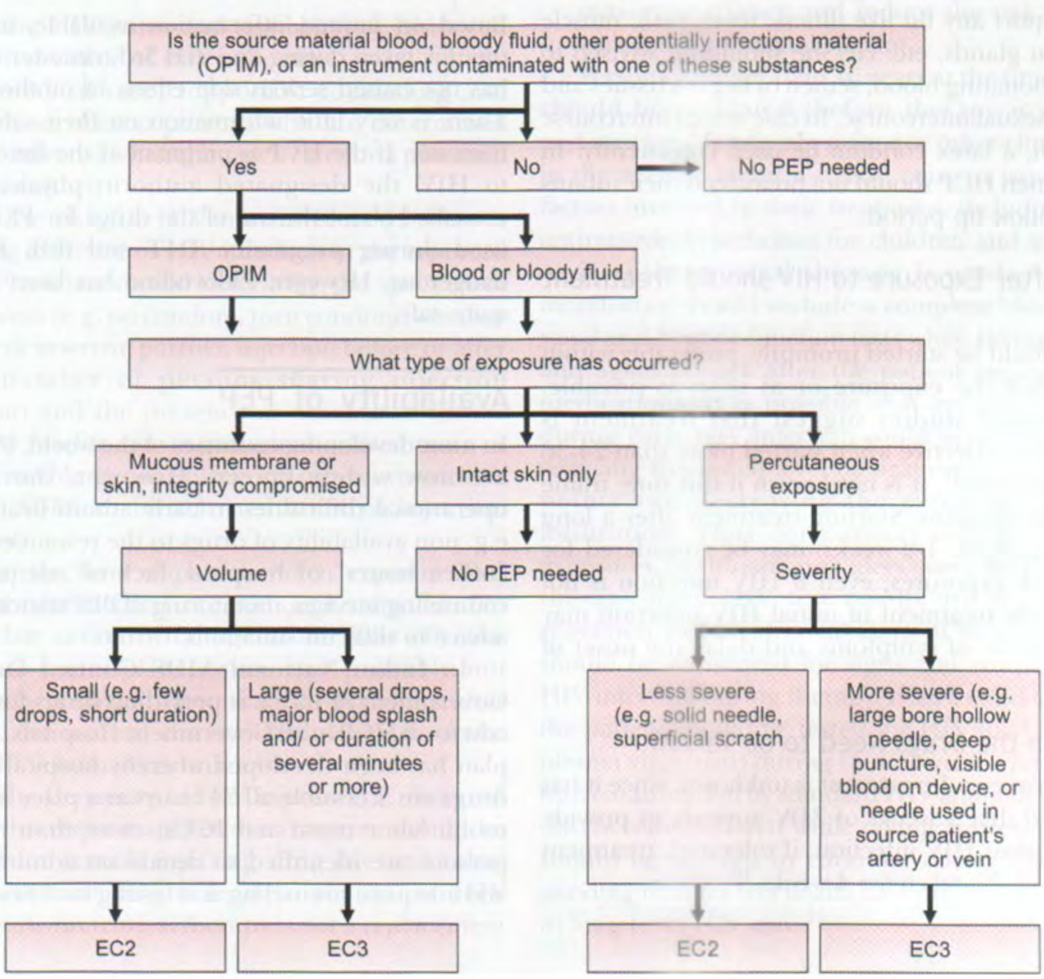
Data from various centers suggest that using three drugs regimen is associated with increased adverse events vs 2-drug regimen. With the availability and tolerability of the new agents there is a debate on the use of new agents, e.g. emtricitabine/tenofovir has largely replaced lamivudine/zidovudine as a regimen back bone in chronically infected individuals. In addition, more recently introduced PIs, such as darunavir /ritonavir, lopinavir/ritonavir and atazanavir/ ritonavir offer improved efficacy and tolerability profiles as compared to the earlier PIs.

However, due to relatively lesser number of HIV infected individuals on triple therapy and an overall low prevalence of HIV in India, presently the above guidelines are being followed. The physicians dealing with HIV medicines may modify these guidelines depending on the source, risk and their experience.

Flow chart 5.5.1: To determine HIV status code (HIV SC)



Flow chart 5.5.2: To determine exposure code (EC)



What About Exposure to Blood for which the HIV Status of the Source Person is Unknown?

If the source individual cannot be identified or tested, decisions regarding follow-up should be based on the exposure risk and whether the source is likely to be a person who is HIV positive. Follow-up HIV testing should be available to all workers who are concerned about possible HIV infection through occupational exposure.

Testing and Counseling Following Exposure

The exposed HCP is tested for HIV immediately following exposure, at six weeks following exposure and again at twelve weeks after the exposure. On all the occasions, HCP must be provided with a pre-test and post-test counselling. HIV testing should be carried out as per the strategies of testing described elsewhere. A complete blood count, renal function and liver function tests should be done 2 weeks after starting treatment. HCP should be advised to report any flu like illness, fever, rash, muscle aches, swollen glands, etc. He/She should be advised to refrain from donating blood, semen or organs/tissues and abstain from sexual intercourse. In case sexual intercourse is undertaken, a latex condom be used consistently. In addition, women HCP should not breastfeed their infants during the follow up period.

How Soon after Exposure to HIV should Treatment Start?

Treatment should be started promptly, preferably within 1–2 hours after the exposure or as soon as possible. Although animal studies suggest that treatment is substantially less effective when started more than 24-36 hours after exposure[3], it is not known if this time frame is the same for humans. Starting treatment after a long period (for example, 1-2 weeks) may be considered for the higher risk exposures; even if HIV infection is not prevented, early treatment of initial HIV infection may lessen the severity of symptoms and delay the onset of AIDS.

How Long do the Drugs Need to be Taken?

The optimal course of treatment is unknown; since it has been observed that 4 weeks of ZDV appears to provide protection against HIV infection, if tolerated, treatment should probably be taken for 4 weeks.[10]

How Safe are these Drugs?

While administering PEP, the important goal is completion of a 4 week PEP regimen. So the toxicity profile of drugs used is a relevant consideration. NRTIs are associated mainly with gastrointestinal side effects like nausea, diarrhea, etc. however ddI has been associated with fatal and nonfatal pancreatitis among HIV infected patients treated for more than 4 weeks. The use of PI has been shown to be associated with rise in blood sugar, triglycerides, IDV with nephrolithiasis (so ensure more water intake), NFV with diarrhea, NVP with hepatotoxicity and EFV with dizziness, insomnia, etc. All these drugs have interactions with other drugs also.

It has been observed that 50 percent of HCP experience adverse symptoms like nausea, malaise, anorexia and headache while taking PEP with approximately 33 percent stop taking PEP due to adverse signs and symptoms.[3] The side effects are more among HCP taking three drug regimen as compared to those on two-drug regimen. NVP has been associated with serious hepatic toxicity in a number of cases and is no longer recommended for PEP.[11]

Should Pregnant Women Take these Drugs?

Based on limited information available, anti-retroviral therapy taken during 2nd and 3rd trimester of pregnancy has not caused serious side effects in mothers or infants. There is very little information on their safety in the 1st trimester. If the HCP is pregnant at the time of exposure to HIV, the designated authority/physician must be consulted about the use of the drugs for PEP. EFV is not used during pregnancy. D4T and ddI, IDV may be dangerous. However, Zidovudine has been found to be quite safe.

Availability of PEP

In most developing countries of the world, PEP regimens are now widely known. However, there might be operational difficulties in early administration of drug, e.g. non availability of drugs to the resource person after "office hours" of hospital, lack of adequate testing/ counseling services, monitoring of PEP toxicity and expert advice in difficult situations.

In India, National AIDS Control Organisation, Government of India, is providing drugs for PEP free of cost to all HCP in all Government Hospitals. An extensive plan has been developed whereby hospital ensures that drugs are accessible all 24 hours at a place in emergency room, labor room and ICUs; more than one resource persons are identified to decide on administering PEP and adequate counseling and testing facilities are available

to all categories of HCP. A proper "exposure report" is made in a predesigned form and full follow-up of HCP for at least six months is ensured.

Occupational Exposure Management Resources

Following situations are anticipated wherein an **expert** consultation is sought for PEP:

- Delayed exposure report (more than 24-36 hours)
- Unknown source (needle in sharp disposal container or laundry)
- Pregnant (or suspected pregnant) HCP
- Likely resistance of source virus to antiretroviral agents
- Toxicity of initial PEP regimen

Considerations in Initiating Antiretroviral Therapy for PEP

Physicians considering the initiation of antiretroviral therapy in an attempt to reduce the risk for HIV infection in an exposed person should take the following steps in consultation with an expert in the use of antiretroviral agents:

- Evaluate the HIV status and risk behavior history of the reported source of HIV exposure.
- Provide medical care, supportive counseling and prevention services to persons who are determined to be HIV infected when they seek care for a potential HIV exposure.
- Evaluate the risk for HIV transmission (if there is convincing evidence of HIV infection in the reported source). Physician should determine the specifics of the risk event (e.g. no condom, torn condom, whether receptive or insertive partner, injection before or after others, number of persons sharing injection equipment) and the presence or absence of factors that would modify risk (e.g. vaginal or anal tears or bleeding, visible genital ulcers or other evidence of an active STD, or bleach treatment of injection equipment).
- Determine the time elapsed between exposure and presentation for medical care. Although animal studies indicate that antiretroviral agents are most effective within 1–2 hours of exposure and probably not effective when started later than 24–36 hours after exposure, the interval during which therapy can be beneficial for humans is unknown.
- Evaluate the frequency of HIV exposure. Uninfected persons who request antiretroviral agents should be evaluated for sexual, injecting drug use and other behaviours that might lead to recurrent HIV exposures. Antiretroviral therapy is not a replacement for adherence to behaviours that reduce the risk of HIV exposure.

Provide counseling and obtain informed consent. Because postexposure prophylaxis is an experimental therapy of unproven efficacy, informed consent should be obtained and recorded in the medical charts of all persons prescribed antiretroviral agents following non-occupational exposure. Such consent should document the patient's understanding of:

- The need to initiate or resume relevant HIV risk-reduction behaviors (e.g. condom use and /or drug treatment)
- The limited knowledge about the effectiveness and toxicity of antiretroviral treatment for non-occupational exposure
- The known side effects of the medications being prescribed
- The name and phone number of a source for follow-up medical care
- The frequency and timing of recommended follow-up HIV testing
- The signs and symptoms associated with acute HIV seroconversion
- The need for adherence to prescribed medications to maximize efficacy and reduce the risk for infection with a drug resistant variant.

Persons younger than 16 years at the time of exposure should be evaluated (before therapy is initiated) by pediatricians, family physicians or other clinicians expert in the specific medical needs, consent issues and other factors involved in their treatment, including the use of antiretroviral medicines for children and adolescents.

If anti-retroviral therapy is used, drug toxicity monitoring should include a complete blood count and renal and hepatic function tests when therapy is initiated and again 2 week after the patient begins to take the medications. It is possible that antiretroviral therapy during early HIV infection could benefit the patient by reducing the initial level of viral replication (i.e. the set point) and decreasing the extent of lymph node infiltration. Thus, for patients with the highest risk exposures, health care providers may consider continuing therapy until HIV test results are received from a specimen drawn after 28 days of treatment. Patients should be monitored for signs and symptoms of acute HIV infection during therapy. If such conditions develop, the patient should be tested for HIV (p24 antigen, HIV plasma viral load) during their 4-week course of therapy with confirmation by standard HIV antibody tests. Persons who become infected while taking antiretroviral therapy should be advised to continue taking the medication pending transfer to a health care provider who specializes in long term HIV care.[12]

Postexposure Prophylaxis Following Non-Occupational Exposure to HIV

The topic of Nonoccupational exposure is being discussed but the current guidelines clearly recommend that PEP is to be used for occupational exposure only.

Increasingly HIV PEP is now also prescribed in non-occupational settings. These include sexual assault, consensual unprotected sex, injecting drug use, and needle-stick or sharp object injuries in persons other than healthcare professionals, is mostly involving young adolescents who are experimenting and indulge in risky behavior. Rationale for its use is derived on the following supportive information.

Potential HIV exposures in children occur most often by accident (e.g. needlesticks in the community, fights, or playground incidents resulting in bleeding by an HIV infected child) or by sexual abuse or assaults.[13] In a review of charts from 1 year in the pediatric emergency department of one hospital, 10 children considered for nPEP were identified (six because of sexual assault and four because of needlestick injuries). Eight began taking nPEP, but only two completed the 4-week course.[14] An analysis of 9,136 reported acquired immunodeficiency syndrome cases in children identified 26 who were sexually abused with confirmed or suspected exposure to HIV infection.[15]

The American Academy of Pediatrics has issued nPEP guidelines for pediatric patients.[16] Ensure appropriate dosing for drugs that do not have capsule/tablet formulations that allow pediatric dosing. Drugs for which pediatric formulations are available might need to be prescribed. Adherence to the prescribed medications will depend on the involvement of, and support provided to, parents or guardians.

Nonoccupational exposure was defined as unprotected sex, sharing of injection equipment or any other exposure to potentially contaminated blood through needle injuries, bites or fights. PEP, based on a three-drug regimen, is offered following anal or vaginal intercourse with a person known to be HIV-positive or at increased risk of infection (e.g. injecting drug users, men who have sex with men) and following sharing of IDU equipment. PEP is not offered for oral sex with a partner of unknown serostatus. PEP can be offered, according to risk factors of HIV transmission (high infectivity of the source partner, sexually transmitted diseases, traumatic sexual intercourse or menstruation) following vaginal intercourse with a partner of unknown HIV status and for any oral sex with a partner known to be HIV-positive or at increased risk.

Recommendations for nonoccupational PEP are available in both Europe and the USA. The transmission rate for HIV infection after a single sexual encounter between two consenting adults is low, estimated to be 0.01–0.2 percent. However, in child sexual abuse, because of the increased incidence of violence and trauma, the immature, thin vaginal epithelium, and cervical ectopy, the risk of transmission is likely to be much higher. In countries where the community prevalence of HIV infection is high, the risk of transmission of HIV infection through child sexual abuse is likely to be further increased, although data on the actual risk is difficult to obtain.

Evidence of Possible Risks from nPEP

Concerns about the potential risks from nPEP as a public health intervention include possible decrease in risk-reduction behaviors resulting from a perception that postexposure treatment is available, the occurrence of serious adverse effects from antiretroviral treatment in otherwise healthy persons, and potential selection for resistant virus (particularly if adherence is poor during the nPEP course). Evidence indicates that these theoretical risks might not be major problems.

The availability or use of nPEP might not lead to increases in risk behavior. Of participants in the nPEP feasibility study in San Francisco, 72 percent reported a decrease in risk behavior over the next 12 months relative to baseline reported risk behavior, 14 percent reported no change, and 14 percent reported an increase.[17] However, 17 percent of participants requested a second course of nPEP during the year after the first course, indicating that although participants did not increase risk behaviors, a substantial proportion of the participants did not eliminate risk behaviors.

Nonoccupational PEP is reported it to be cost-effective only in situations in which the sex partner source was known to be HIV infected or after unprotected receptive anal intercourse with a homosexual or bisexual man of unknown serostatus.[18] Even if nPEP is cost-effective for the highest risk exposures, behavioral interventions are more cost-effective. This emphasizes the importance, when considering nPEP, of providing risk-avoidance and risk-reduction counseling to reduce the occurrence of future HIV exposures; requires prompt evaluation of patients and consideration of biomedical and behavioral interventions to address current and ongoing health risks. This evaluation should include determination of the HIV status of the potentially exposed person, the timing and characteristics of the most recent exposure, the frequency of exposures to HIV, the HIV status of the source, and the likelihood of concomitant infection with other pathogens or negative health consequences of the exposure event.

If the source persons known to be HIV infected are at risk for acquiring HIV infection and should be considered for nPEP if they seek treatment within 72 hours of exposure. If possible, source persons should be interviewed to determine his or her history of

antiretroviral use and most recent viral load because this information might provide information for the choice of nPEP medications. When the HIV status of the source is unknown, it should be determined whether the source is available for HIV testing. If the risk associated with the exposure is considered substantial, nPEP can be started pending determination of the HIV status of the source and then stopped if the source is determined to be noninfected.

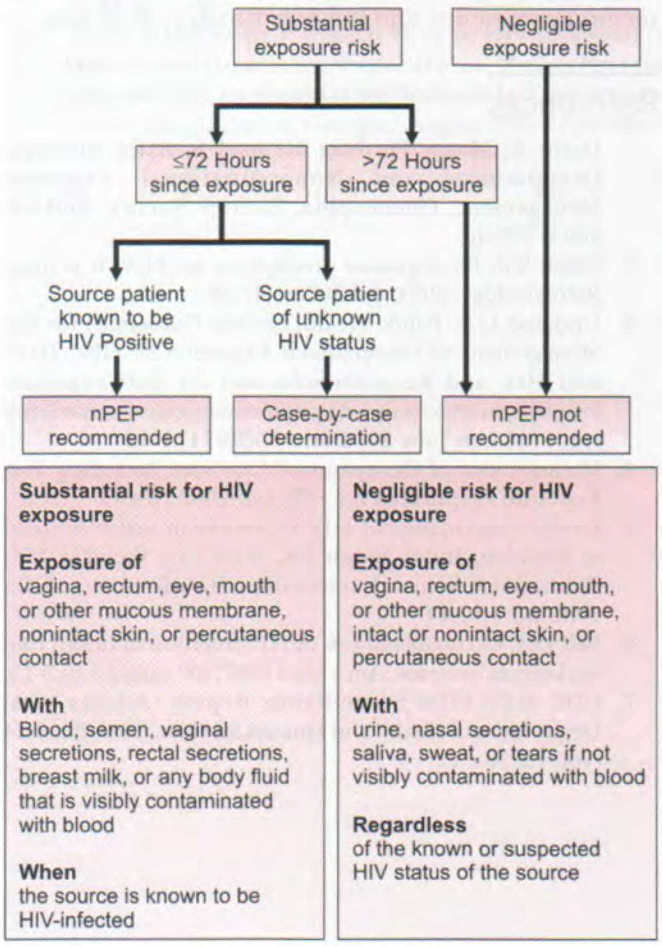
Recommendations for Use of Antiretroviral nPEP

A 28-day course of HAART is recommended for persons who have had nonoccupational exposure to blood, genital secretions, or other potentially infected body fluids of a person known to be HIV infected, when that exposure represents a substantial risk for HIV transmission and when the person seeks care within 72 hours of exposure.

When indicated, antiretroviral nPEP should be initiated promptly for the best chance of success (Flow chart 5.5.3).

For persons who have had nonoccupational exposure to potentially infected body fluids of a person of unknown

Flow chart 5.5.3: Algorithm for evaluation and treatment of possible nonoccupational HIV exposures



HIV infection status, when that exposure represents a substantial risk for HIV transmission and when care is sought within 72 hours of exposure, no recommendations are made either for or against the use of antiretroviral nPEP. Clinicians should evaluate the risk for and benefits of this intervention on a case-by-case basis.

Follow-up Testing and Care

All patients seeking care after HIV exposure should be tested for the presence of HIV antibodies at baseline and at 4-6 weeks, 3 months, and 6 months after exposure to determine whether HIV infection has occurred. In addition, testing for sexually transmitted diseases, hepatitis B and C, and pregnancy should be offered.

Although nPEP might reduce the risk for HIV infection, it is not believed to be 100 percent effective. Therefore, patients should practice protective behaviors with sex partners (e.g. abstinence or consistent use of male condoms) or drug-use partners (e.g. avoidance of shared injection equipment) throughout the course of nPEP to avoid transmission to others if they become infected, and after nPEP to avoid future HIV exposures.

At follow-up visits, clinicians should assess their patients' needs for behavioral intervention, education and services. This assessment should include frank, nonjudgmental questions about sexual behaviors, alcohol use and illicit drug use. Clinicians should help patients identify ongoing risk issues and develop plans for improving their use of protective behavior.

Considerations for Vulnerable Populations

Pregnant Women and Women of Childbearing Potential

Administering HAART of short course of ARV to the mother is also a form of nPEP for the unborn child. Currently safe and appropriate use of antiretroviral medications during pregnancy, either for the benefit of the HIV infected woman's health or to prevent transmission to newborns have been developed that is able to bring down the incidence of HIV transmission from 30 percent to less then 2 percent.

Children

Sexual Assault Survivors

Use of nPEP for sexual assault survivors has been widely encouraged both in the United States and elsewhere, Sexual assault is relatively common among women: 13 percent of a national sample of adult women reported having ever been raped (60% before age 18), and 5 percent reported having been raped more than once.[19]

Sexual assault typically has multiple characteristics that increase the risk for HIV transmission if the assailant is infected. In one prospective study of 1,076 sexual assault cases, 20 percent were attacked by multiple assailants, 39 percent were assaulted by strangers, 83 percent of females were vaginally penetrated, and 17 percent overall were sodomized. Genital trauma was documented in 53 percent of those assaulted, and sperm or semen was detected in 48 percent. In another study, in which toluidine blue dye was used as an adjunct to naked-eye examination, 40 percent of assaulted women (70% of nulliparae) had detectable vaginal lacerations, compared with 5 percent of women examined after consensual sex.[20]

Patients who have been sexually assaulted will benefit from 28 days of ARV and supportive services to improve adherence to nPEP if it is prescribed, and from psychological and other support provided by sexual assault crisis centers. All sexually assaulted patients should be tested and administered prophylaxis for sexually transmitted infections, and women who might become pregnant should be offered emergency contraception[21]

Injection-Drug Users

A history of injection-drug use should not deter clinicians from prescribing nPEP if the exposure provides an opportunity to reduce the risk for consequent HIV infection. A survey of clinicians serving injection-drug users determined a high degree of willingness to provide nPEP after different types of potential HIV exposure.

In judging whether exposures are isolated, episodic, or ongoing, clinicians should consider that persons who continue to engage in risk behaviors (e.g. commercial sex workers or users of illicit drugs) might be practicing risk reduction (e.g. using condoms with every client, not sharing syringes, and using a new sterile syringe for each injection). Therefore, a high-risk exposure might represent an exceptional occurrence for such persons despite their ongoing risk behavior.[23]

Injection-drug users should be assessed for their interest in substance abuse treatment and their knowledge and use of safe injection and sex practices. Patients desiring substance abuse treatment should be referred for such treatment. Persons who continue to inject or who are at risk for relapse to injection-drug use should be instructed in the use of a new sterile syringe for each injection and the importance of avoiding the sharing of injection equipment. In areas where programs are available, health-care providers should refer such patients to appropriate sources of sterile injection equipment.

Summary

In the HIV Prevention program, PEP is a powerful tool used by all national and international service providers. Mostly it is agreed that high risk exposure from a known or suspected HIV infected source individual should be treated with 28 days of 2 or 3 drug regimen and the treatment can be initiated with in 72 hours of exposure. Serial testing at baseline, 4 to 6 weeks, 12 weeks and 25 weeks post exposure should be performed. If the source individual is available for testing, a negative source HIV ELISA, in the absence of history, signs or symptoms consistent with recent exposure or acute HIV viral infection, should allow discontinuation of PEP for the exposed individual.

Critical issues in relation to Non Occupational exposures as quantifying exposure, efficacy, safety, and effects on risk behaviors are being studied in careful controlled clinical trials in a variety of high-risk populations. Cost effectiveness analyses using computer based models of HIV infection suggest that with the current drug cost, nPEP may be cost effective only if targeted at extremely high risk young population.[24] Issues of who will pay for HIV prevention treatment and services, including drug cost, remain subject of debate in the medical community and the policy makers as of now.

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5.6

Managing Failing ART Regimens in Children

Tammy Meyers

Epidemiology

As antiretroviral treatment (ART) programs are successfully scaled up globally, addressing the issues of prevention and management of treatment failure becomes increasingly critical. Reports on the rates of therapy failure and treatment switches occurring in low-and middle-income countries (LMIC) are increasing in the literature. In general, relatively few patients are changing to second line with rates of 2.9 percent described in the sub-Saharan African region.[1] Where viral load monitoring (VL) is available however, patients are generally switched to second-line therapy earlier and at higher CD4 counts than where VL is unavailable.[1] There are fewer data in the context of pediatrics. In Kampala, Uganda, where children received nevirapine (NVP) as part of the first line regimen, 26 percent developed treatment failure within 12 months of starting therapy.[2] In South Africa, where ritonavir-boosted lopinavir (LPV/r) is generally used as part of first line therapy in children <3 years and efavirenz (EFV) in children >3 years, among a cohort of over 5000 children from various centers around the country, 11.2 percent of children developed treatment failure (defined as two consecutive viral load results >10000 copies/ml after 24 weeks of therapy).[3] Less than half of these children, remaining in care a year after failure was diagnosed, were switched to second line therapy.

Current Treatment Recommendations and Implications for Future Options

Nevirapine (NVP) has been widely used as a single dose to mother and infant, and more recently as part of combination therapy for prevention of mother-to-child transmission of HIV (PMTCT). Nevirapine resistance mutations reportedly occur in up to 52.6 percent of children subsequent to the use of single dose NVP for PMTCT.[4] Combination therapy for PMTCT and covering the tail with zidovudine and lamivudine may reduce the proportion of children acquiring resistance mutations, although NVP resistance is still likely to develop.[5] NVP resistance mutations cross react with efavirenz (EFV), and these mutations can reduce efficacy of future ART regimens containing either non nucleoside reverse transcriptase inhibitor (NNRTI).[6]

WHO now recommends that all children <1 year of age be commenced on ART regardless of clinical and CD4 count and countries are advised that, where available, boosted protease inhibitors (bPIs) be used as part of first line therapy.[7] Recent data released from the IMPAACT P1060 trial confirm that NVP resistance reduces efficacy of a NVP-containing regimen compared to a regimen containing bPI.[8]

In December 2008, 78 percent of the world's children receiving ART were taking a NVP-containing regimen.[9] Boosted protease inhibitors are more expensive than NNRTIs, less palatable and require the presence of a cold chain. They are therefore not readily available in many LMIC.

Given the fact that infants continue to be exposed to NVP through PMTCT and with the results of the P1060 study, treatment failure among many children on NNRTI-based therapy is anticipated. In Uganda as discussed above, where NNRTI-based treatment is used first line, more than a quarter of children compared to 14 percent of adults had failed ART by 12 months.[2] In Chang Mai, Thailand, among children who failed first line NNRTI-based treatment most (82%) children did so within 48 weeks of starting therapy and with high proportions found to have major NNRTI and NRTI resistance mutations.[10] Similar resistance patterns have been reported among children failing NNRTI-based therapy in Mozambique.[11]

Treatment Failure in Children

The definition of treatment failure is challenging and varies between rich countries and LMIC. In 2006, WHO guidelines recommended the use of clinical and immunological criteria on which to determine treatment failure.[12] Treatment failure was considered when either new or recurrent stage 3 or 4 clinical events develop in a child on at least 6 months of therapy or when there is a drop in the CD4 to values at or below their age-related CD4 threshold for the initiation of treatment after initial immune recovery following the initiation of ART. Switching a regimen was recommended when CD4 values fell to below 15 percent (12-35 months of age), 10 percent (36-59 months of age), or 100 cells/mm^3 (>5 years of age). Immunological criteria for recognizing treatment failure were supplemental to clinical criteria. As viral load levels have not been routinely monitored, viral load values alone were not used for defining treatment failure in children. In the United States, where virological monitoring is routine, treatment failure is defined first and foremost as an incomplete viral response of less than 1.0 log reduction in viral load from baseline after 8 to 12 weeks on therapy, or a repeat viral load greater than 400 copies/ml after 6 months of ART.[13]

At a recent WHO guidelines revision meeting (Dec 2009) it was agreed that viral load testing aimed at determining virological failure and guiding decisions about regimen switches would be included in updated guidelines; updated guidelines are pending. In the DART study where clinical monitoring of patients was compared with clinical as well as laboratory monitoring, excellent survival was reported among adults in both groups. Regimen switching occurred at a higher rate in the second year in those who had CD4 monitoring.[14] Viral load testing was not conducted. Several studies have demonstrated the unreliability of clinical or immunological criteria to predict virological failure in both children and adults resulting in either delayed switching or unnecessary transition to second line therapy.[10, 15] Development of increasing numbers of resistance mutations the longer a child is exposed to a nonsuppressive regimen is likely, thereby compromising future treatment options.

Viral load monitoring may be used routinely to detect early virological failure in which case it is recommended to be conducted at regular 6-monthly intervals. Some countries are planning to use viral load in a targeted manner to confirm failure when there are clinical or immunological indications of this. In the targeted approach, viral load may be used early in the first 4 to 6 months after starting ART as an adherence tool and subsequently only once there are signs of clinical or immunological failure [WHO guidelines advise this but are not yet published].

There is some evidence among adults that in the absence of other reasons for virological escape, a confirmed viral load between 5000 to 10000 copies/ml correlates with clinical and immunological failure.[16] Virological failure is defined in the updated WHO guidelines as a viral load above 5000 copies/ml for both adults and children. Results are anticipated shortly from the PENPACT 1 study whose aim, among others, was to compare switching therapeutic regimens among children failing therapy at VL of 1000 copies/ml as opposed to 30000 copies/ml, whether this will change viral load limits at which to switch remains to be seen.

Management of Treatment Failure

A full assessment should be conducted of the possible reasons for failure; poor adherence is most likely, but inadequate drug exposure as a result of: drug interactions, incorrect or underdosing and poor drug absorption may occur.

Adherence

Poor adherence to ART is the most important reason why treatment failure occurs. In order to achieve maximum viral suppression, adherence levels close to 100 percent of scheduled doses are required.[17,18] When a non-suppressive regimen is continued, resistance mutations accumulate. Evidence suggests that development of resistance is more rapid when patients fail first-line NNRTI-based therapy as compared to bPI therapy.[19] Prior to switching to second line therapy however, efforts should be made to address adherence.

In attempting to prevent or determine the reasons for treatment failure as a consequence of poor adherence, the following factors might be helpful:

Health care provider issues

- Education of parents or care-providers; treatment education should ideally be conducted prior to the start of ART in which the reasons for excellent treatment adherence on an indefinite basis must be explained and emphasized. Ongoing treatment support and education is recommended at each visit.
- A good health care provider-patient relationship underpins adherence
- If virological failure is detected, early intervention to improve adherence is likely to be helpful.

Patient factors

- Social issues which may impact adherence should be addressed as appropriate.
- The caregiver should ideally identify and disclose to one other person in the home who can help with treatment (treatment buddy) as a back-up and to enhance the treatment support.

- A different caregiver accompanying the child to each appointment, is a warning sign that consistent adherence might be compromised, this requires exploration.

Medication-related issues

- Solid formulations are generally easier to use and may be better tolerated; children should be taught to take pills as early as possible (from >4 years of age)
- Dosages of liquid formulations if used should be rounded up to a convenient volume
- Syringes for liquid formulations should be marked at the correct dosage with a blade or permanent marker. Show the caregiver how to draw up the correct volume and expel excess air
- The syringe and the medicine for which it is used should be color coded with the same color to prevent mixing of medications and doses
- Ensure that caregiver's eyesight is adequate to accurately administer medication
- Teach caregivers to open child proof containers
- Medications should fit into the patient lifestyle. For example twice daily medication does not have to be given strictly 12-hourly, rather at a convenient time. It is far better to give a dose later than usual rather than not give the medication at all
- It is useful to monitor if treatment is being collected.

Drug Interactions

Drugs from the non-nucleoside reverse transcriptase inhibitor (NNRTI) and from the protease inhibitor (PI) classes are metabolised by the cytochrome-P450 (CYP450) pathway in the liver. Pharmacokinetic levels of these drugs may be altered when coadministered with CYP450 inhibitors or inducers. Of particular concern when considering treatment failure are drugs which induce CYP450, as substrate levels such as NNRTIs and PIs may be lowered resulting in inadequate therapeutic levels of antiretroviral agents.[20] Drugs that interact in this way include: rifampicin, carbamazepine, phenytoin, phenobarbitone and alcohol. In LMIC, where tuberculosis (TB) is prevalent, drug interactions between ART and TB treatment are of particular concern with rifampicin being the agent most implicated. Rifampicin is an essential component of short course combination TB treatment in LMIC. There have been several pharmacokinetic studies in children to determine the optimal dosing of ART agents coadministered with rifampicin-containing TB therapy. Among the NNRTIs, efavirenz levels are less affected by rifampicin than nevirapine levels.[20] In children who are less than 3 years of age and for whom efavirenz dosing has not yet been established, "superboosted" lopinavir/ritonavir (LPV/r) can be used together with rifampicin-containing TB treatment. Extra ritonavir is administered so that the ratio of lopinavir to ritonavir becomes 1:1.[21] Nonboosted PIs, e.g. ritonavir as a single agent are not recommended and have been implicated in the development of major PI resistance.[22]

Dosing Issues

Failure to increase the dose of medication in the presence of growth will result in inadequate therapeutic drug levels and result in treatment failure. Poor absorption of drugs may occur when there is severe or chronic gastroenteritis, vomiting. There are no data to guide optimal dosing in these situations, but the clinician should be aware of these factors which may be implicated in treatment failure in children.

Switching Therapy

Once treatment failure is established and the reasons for this addressed, it is preferable to switch to a regimen containing 3 or at least 2 active agents. Treatment history combined with resistance testing is helpful in determining a future regimen for a child. However, where resistance testing is unavailable, decision-making about switching of a regimen will depend on the prior regimen that the patient was taking and what is locally available. Second-line treatment choice will be determined by whether the child is failing an NNRTI- or PI- based regimen.

When NNRTI resistance has occurred there is generally no place for maintaining patients on the same regimen, the longer the regimen is maintained the more NRTI resistance mutations are likely to accumulate, limiting future treatment options.[19] Among adults failing a fixed dose combination stavudine/lamivudine/nevirapine regimen who also had genotyping, there were no good treatment options available for almost half, because of the major resistance mutations that emerged.[23] Increased mortality associated with maintaining patients on a failing NNRTI regimen has been demonstrated in an adult study.[24] Once the reasons for treatment failure have been addressed, the regimen should ideally be changed to a boosted PI with two active NRTIs.

Patients who fail a bPI regimen and who have never received single PI (e.g. ritonavir alone) may have no PI and minimal NRTI mutations in which case the original regimen may be continued. In Johannesburg, South Africa treatment resistance data reported from two large pediatric cohorts where some children were failing a first line bPI regimen, only low level PI resistance was found in a small proportion of children, the rest were found to have no PI mutations.[25, 26] If there has been no prior NNRTI exposure and if there are few NRTI resistance

mutations (where resistance testing done), simple switch to 2 NRTIs and an NNRTI may be appropriate. However, patients with multiple PI mutations may only achieve viral control when another boosted PI is used. Recently newer PIs darunavir and tipranavir demonstrate improved control in this situation.[27]

Choice of NRTI backbone for second line depends on what was used for first line therapy and whether treatment switch was rapid or delayed. The longer patients who are receiving the NRTI thymidine analogues (stavudine/zidovudine) remain on the failing regimen, the more thymidine analogue mutations (TAMs) are likely to increase.[11] Where resistance testing is unavailable and where targeted viral load use is planned the sequencing of NRTIs should be carefully considered.

Despite evidence that the M184V mutation associated with lamivudine (3TC) failure reduces viral replication ability and viral fitness and enhances susceptibility to zidovudine, stavudine and tenofovir,[28] clinical research has not demonstrated that the retention of lamivudine in second line therapy is beneficial. One randomized control trial has been conducted to examine this issue which found no significant difference in the reduction of HIV RNA in individuals who maintained lamivudine in their second line regimen compared to those who did not.[29] In spite of this lamivudine is frequently maintained in second line regimens. No studies have been reported on failing abacavir or tenofovir containing first line regimens (Table 5.6.1).

Holding Regimens

In some situations, especially among adolescents, where adherence is troublesome and clinicians are reluctant to commence a second-line regimen, holding regimens have been attempted. There is insufficient evidence for this approach although the use of lamivudine monotherapy in this situation yielded promising results in a small adult study.[30] Further research is required before this can be widely advocated. In another approach, a PI and NNRTI-sparing regimen trizivir (ZDV + 3TC + ABC) together with tenofovir prevented immunogical decline and delay in viral evolution in 28 heavily experienced adults.[31]

Resistance Testing

Clinical evaluation including history of previous drug exposure is essential for guiding decisions about future treatment. Drug resistance testing may assist with choice of a new regimen once treatment failure has been diagnosed. Although generally unavailable for use in many LMICs, low cost technology for viral resistance testing and the use of dried blood spots (DBS) for this purpose is being developed and is likely to become more readily available in the future.[32, 33] Genotyping and phenotyping for resistance have been shown to be helpful in predicting response to new regimens.[34] However, genotyping has been the preferred technique as it is generally less complicated, more affordable and has a quicker turn-around time for results. Genotyping does have shortcomings and may underestimate the level of resistance as most techniques are unable to detect resistance in minority populations of virus.[35] Bioinformatic systems are in development which generate mathematical models using genotyping for predicting phenotyping and response to treatment.[36] It is generally recommended that resistance testing be done whilst the patient is still taking antiretroviral as wild-type virus can re-emerge when off therapy and mask the mutant virus.

Lamivudine and the currently available NNRTIs (NVP and EFV) have a low genetic barrier to development of resistance, usually requiring the presence of one mutation to confer resistance. Therefore, the most likely mutations to develop early in children failing an NNRTI-based regimen are those of lamivudine (M184V) and NNRTI (K103N and Y181C). Thymidine analogue mutations (TAMs) to stavudine and zidovudine accumulate more slowly and with increasing numbers of TAMs the more

Table 5.6.1: First line regimens and options for switching after treatment failure diagnosed

	First Line Agents	*Second Line Agents*	*Comments*
NRTI	AZT or d4T+3TC ABC+3TC	ABC /3TC+ddI d4T or AZT +3TC	If on NNRTI-based regimen and treatment switched early, TAMS unlikely to have accumulated
NNRTI	NVP/EFV	LPV/r	Failing NNRTI regimen, switch treatment early once contributing factors (e.g. adherence) addressed
Boosted PI	LPV/r	Continue same regimen If no prior NNRTI exposure and no TAMS, NNRTI-containing regimen may be appropriate Major PI resistance mutations, boosted PI (eg darunavir approved for children >6years)) or new class agents when dose is approved for children.	May not develop resistance even in the face of virological failure Genotyping, if available, may be helpful to guide treatment choice.

likely NRTI resistance will occur. If treatment is switched quickly in the absence of resistance testing, standard of care second line regimens are likely to be effective. Genotyping can be helpful in patients who have remained on a failing NNRTI-containing regimen for some time. However, unless treatment alternatives are readily available genotyping will be redundant.

Boosted protease inhibitors have a high genetic barrier to resistance and when children fail a first line bPI-containing regimens there is evidence that major PI resistance is unlikely to occur.[22, 26] Absence of previous NNRTI exposure and TAMs as detected by genotyping would be useful in guiding a switch to an NNRTI-based regimen which would be appropriate under these circumstances. However, if nonboosted PIs have been used, e.g. ritonavir alone, major PI mutations may emerge and resistance testing will be helpful to determine optimal subsequent regimens. In this case boosted PIs or newer classes of drugs are recommended.

Where resistance testing is unavailable, consideration must be given to sequencing of regimens in such a way that minimal cross resistance can occur between the first and second-line therapy options. Using an abacavir/lamivudine NRTI backbone could spare thymidine analogues for second line therapy. Boosted PIs as part of first line therapy will also minimize development of resistance so their use early in children as recommended by WHO is also helpful in prevention of development of major resistance.

New Drugs in the Pipeline for Pediatric Use

Novel agents and new classes of drugs continue to be developed. Although, there is a time lag between adult and pediatric trials, some new formulations have been approved for pediatric use and several are currently undergoing dose-finding investigation in children. It is important for clinicians to be aware of these developments and as new agents are approved to consider which may be most appropriate in sequencing of regimens over time. Newer agents are likely to be costly, and this will impact availability for large programs in LMIC. Nevertheless, factors such as difficulties with TB/HIV cotreatment, and widespread NNRTI resistance make the investigation of these novel agents for pediatric use particularly compeling.

Some of the new agents that are of particular interest in this regard and have undergone or are entering pediatric investigation include:

Second Generation Non-nucleoside Reverse Transcriptase Inhibitors

Etravirine (ETV) which has already been licensed for use in adults. This agent is in phase II trials in treatment experienced children, and is active against HIV strains resistant to Efavirenz, Nevirapine and Delavirdine, having a higher genetic barrier to resistance. ETV plus optimised background regimen (OBR) provided better viral suppression and improved immunological response than OBR alone.[37] TMC-278 (Rilpivirine), with a similarly high genetic barrier to resistance is entering pediatric phase II trials. However, there is gathering evidence that small percentages of children and adults in Sub-Saharan Africa may harbor the mutations to etravirine which may accumulate the longer the patients are left on a failing regimen containing NVP or EFV.[11, 38]

Protease Inhibitors

Darunavir and tipranavir are two new PIs licensed for use in treatment experienced children. Darunavir was licensed in December 2008 by the Food and Drug Administration (FDA). It is a nonpeptide protease inhibitor which binds rapidly to protease at a unique site and disassociates slowly causing a two-fold higher binding strength compared to other PIs. It is therefore potent even against PI resistant strains, and is recommended in salvage regimens, particularly where major resistance mutations have developed as a result of prior single PI use.[27] Darunavir has demonstrated equivalence with LPV/r in drug naïve adults and has a favorable toxicity profile.[39] In developed country settings, DRV/r has been reported to be cost effective compared to LPV/r.[40] Dose-finding pharmacokinetic trials are underway for younger children.

Tipranavir has been licensed for use in children >2 years and treatment failure with darunavir preserves activity of tipranavir and vice versa, although darunavir has lower pill burden and is associated with less serious adverse events.[27]

Integrase Inhibitors

Among this new class of treatment agents, raltegravir has been licensed in adults. Pediatric formulations are currently in phase II trials in treatment experienced children. Generally among those enrolled, raltegravir (RAL) has been well tolerated with few drug related side effects and preliminary data suggest positive CD4 and viral load responses.[41] In individuals with limited treatment options, RAL plus OBR provided better viral suppression than OBR alone for at least 48 weeks.[42,43] RAL is not a CYP substrate, inducer or inhibitor and may therefore be of potential benefit if used together with treatment for TB. A newer agent, elvitegravir, is also entering pediatric trials.

CCR5 Antagonists

This new class of drugs requires CCR5 tropic virus to be effective. Maraviroc has been licensed for use in adults

and pediatric studies are planned. Vicriviroc, the newest CCR5 antagonist is currently being investigated in treatment experienced children. The medication is boosted significantly by ritonavir, and has been shown to be active against strains that are resistant to other medications, including enfuvirtide.

Salvage Therapy

There have been unpublished reports of excess mortality among people failing second-line therapy. In updated guidelines, WHO acknowledges the need for salvage therapy to treat highly experienced adults and children. In this respect some of the newer agents discussed above have demonstrated efficacy in salvage treatment and are likely to play an increasing role in the future. In patients with multidrug-resistant virus who have few remaining treatment options, the combination of RAL, ETV, and DRV/r was well tolerated, and was associated with a rate of virological suppression similar to that expected in treatment-naive patients.[44]

Carefully considered sequencing of treatment regimens may improve durability of first and subsequent therapy and will likely improve treatment outcomes in general. Current global recommendations to start treatment earlier in children are likely to improve outcomes of treatment.[7] It is important to define treatment failure and understand the role that diagnostic techniques such as viral load and genotypic/phenotypic resistance testing play in diagnosis and management of failure. Reasons for treatment failure must be determined so that they can be addressed to prevent failure of future treatment options. However, delays in reacting to treatment failure may unnecessarily compromise subsequent therapy. As new agents and classes of drugs become increasingly available for adults and children, these are likely to improve the management of treatment failure. Diagnostic technology and newer treatment agents are still scarce in LMIC. Clinicians must often work with what is locally available, but should be aware of alternatives. Continued effort to make newer agents and diagnostic procedures more widely accessible in the interest of improving quality of care must occur.

Case Study

Case 1

This is a study of a 7-years-old female who first tested HIV positive on 10/07/2007. She was not given medication for PMTCT as the mother tested HIV-negative during pregnancy. At presentation she had failure to thrive and lymphocytic interstitial pneumonitis, although had never previously been diagnosed with TB and was classified as having WHO stage 3 disease.

She initiated ART 31/08/2007 with a combination of D4T/3TC/EFV. After achieving full viral suppression, in June 2008 it was noted that her viral load had climbed to 26,000 copies/ml. Adherence counseling was provided and it was determined that she had missed 5 days of treatment when she went to visit a family member in a rural village. Adherence was reemphasised but her subsequent viral load in September was 1000 copies/ml. Resistance testing was available and it was noted that she had M184 and K103N (lamivudine and NNRTI resistance), but no TAMs (see: Resistance Test 1).

In managing this patient, the options could include: continuing the current regimen, switching to second line regimen, therapy interruption.

What would you choose to do in this situation?

The K103N single resistance mutation to efavirenz implies that NNRTI treatment failure has occurred. Improved adherence will not reverse this situation, and the longer the patient is maintained on the failing regimen, the more likely it is that TAMs will develop. Nevertheless, since adherence was the reason for treatment failure, the family require intensive counseling in order to ensure that there will be improved adherence with the subsequent regimen. Switching to second line regimen with PI-based therapy is recommended as soon as possible after adherence issues have been addressed. Since there are no TAMS, there is no reason to change the d4T. As discussed above, there is insufficient evidence for keeping 3TC despite the emergence of M184V (3TC resistance mutation) although, in vitro, M184V has been associated with reduced viral replication ability and viral fitness. Indian guidelines recommend retention of 3TC in second line regimens.

After the second viral load the patient was switched to d4T/3TC/LPV/r. Despite ongoing adherence support and counseling, the viral load has not subsequently been suppressed. Further resistance testing was conducted in June 2009 (See: Resistance Test 2).

Date	*CD4*	*VL*
Baseline (10/07/2007)	227 / 6.96%	120000
I + 3 mo (27/11/2007)	453 / 9.29%	<25
19/02/2008	insufficient	<25
15/04/2008	643 /20.6%	Not done
13/06/2008		26000
02/09/2008	833 / 17.8%	1000
31/03/2009	588 / 19.4%	3400
04/05/2009		1500
01/06/2009		5500
19/10/2009	888 / 27.3%	2300
19/03/2010	541 / 17.1%	1000

Resistance Test-1

STANFORD UNIVERSITY
HIV DRUG RESISTANCE DATABASE
A curated public database designed to represent, store, and analyze the divergent forms of data underlying HIV drug resistance.

HOME GENOTYPE-RX GENOTYPE-PHENO GENOTYPE-CLINICAL HIVdb PROGRAM

HIVdb: Genotypic Resistance Interpretation Algorithm

SeqID: 213394.TXT_1 TBN Date: 20-Nov-2008

Summary Data

Sequence includes PR: codons: 1 - 99
Sequence includes RT: codons: 1 - 258
There are no insertions or deletions
Subtype and percent similarity to closest reference isolate:

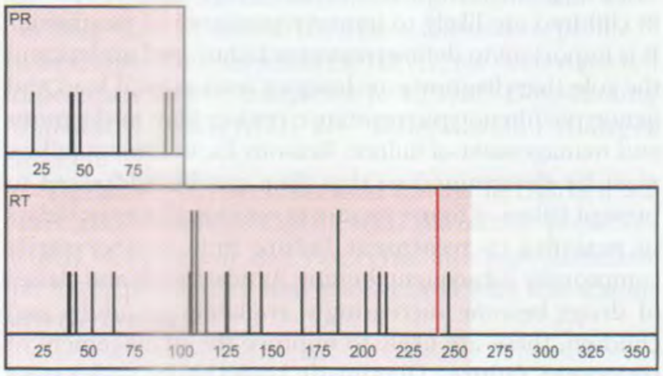
1. PR: C (93.6%)
2. RT: C (93.4%)

Sequence Quality Assessment

Gene	QA Problem	Codons
PR	Stop Codons, Frame Shifts:	None
PR	B,D,H,V,N:	None
PR	Unusual Residues:	None

Gene	QA Problem	Codons
RT	Stop Codons, Frame Shifts:	None
RT	B,D,H,V,N:	None
RT	Unusual Residues:	240

Blue lines indicate differences from consensus B; tall blue lines indicate sites associated with drug resistance.
Red lines indicate QA problems.



Drug Resistance Interpretation

PI Major Resistance Mutations:	None
PI Minor Resistance Mutations:	None
Other Mutations:	I15V, M36I, N37S, R41K, L63S, H69K, L89M, I93L
	Protease Inhibitors
Atazanavir/r (ATV/r)	Susceptible
Darunavir/r (DRV/r)	Susceptible
Fosamprenavir/r (FPV/r)	Susceptible
Indinavir/r (IDV/r)	Susceptible
Lopinavir/r (LPV/r)	Susceptible
Nelfinavir (NFV)	Susceptible
Saquinavir/r (SQV/r)	Susceptible
Tipranavir/r (TPV/r)	Susceptible

PR Comments

- This sequence has 0 major TPV/r-resistance mutations, 1 minor TPV/r-resistance mutations (M36I), and 0 mutations associated with increased TPV/r responsiveness. RESIST study (Baxter J et al, J Virology 2006 and Scherer J et al; EACS 2007).
- M36I/V are weakly associated with PI resistance when present with other mutations. M36I is the consensus amino acid in most non-B subtypes. M36L/T are rare variants of uncertain significance.

Drug Resistance Interpretation

NRTI Resistance Mutations:	M184V
NNRTI Resistance Mutations:	K103N, V106M
Other Mutations:	V35T, E36A, T39E, S48T, V60I, K102Q, V111I, K122E, D123S, I135V, I142V, T165I, K173A, T200E, Q207A, R211K, T240A, V245Q

Nucleoside RTI		Non-Nucleoside RTI	
Lamivudine (3TC)	High-level resistance	**Delavirdine (DLV)**	High-level resistance
Abacavir (ABC)	Potential low-level resistance	**Efavirenz (EFV)**	High-level resistance
Zidovudine (AZT)	Susceptible	**Etravirine (ETR)**	Low-level resistance
Stavudine (D4T)	Susceptible	**Nevirapine (NVP)**	High-level resistance
Didanosine (DDI)	Susceptible		
Emtricitabine (FTC)	High-level resistance		
Tenofovir (TDF)	Susceptible		

RT Comments

- K103N causes high-level resistance to NVP, DLV, and EFV. By itself it has no effect on ETR susceptibility. However, It is an indicator of past NNRTI selection pressure. It also has a synergistic effect with L100I and possibly K101P on ETR susceptibility.
- V106M causes high-level resistance to NVP, EFV, and DLV but does not appear to decrease ETR susceptibility except as a marker of past NNRTI therapy.
- M184V/I cause high-level in vitro resistance to 3TC and FTC and low-level in vitro resistance to ddI and ABC. M184V/I increase susceptibility to AZT, TDF, and d4T.
- M184V partially reverses AZT, d4T, and TDF resistance caused by other AZT mutations (TAMs). AZT mutations in this isolate include: none.

Mutation Scoring

	ATV/r	DRV/r	FPV/r	IDV/r	LPV/r	NFV	SQV/r	TPV/r
Total:	0	0	0	0	0	0	0	0

	3TC	ABC	AZT	D4T	DDI	FTC	TDF	DLV
K103N	-	-	-	-	-	-	-	60
V106M	-	-	-	-	-	-	-	60
M184V	60	12	-8	-5	5	60	-8	
Total:	60	12	-8	-5	5	60	-8	120

The Team

- Who we are and How to contact us
- Publications
- Collaborators
- Acknowledgments

The Data

- User Guide and Database Documents
- Database Statistics
- HIV Related Links
- Additional Resources

Resistance Test-2

STANFORD UNIVERSITY
HIV DRUG RESISTANCE DATABASE

A curated public database designed to represent, store, and analyze the divergent forms of data underlying HIV drug resistance.

HOME GENOTYPE-RX GENOTYPE-PHENO GENOTYPE-CLINICAL HIVdb PROGRAM

HIVdb: Genotypic Resistance Interpretation Algorithm

Report: 268635. TXT Date: 24-Jun-2009 00:33:35 PDT

Seq ID: 268635

Summary Data

Sequence includes PR: codons: 1 - 99
Sequence includes RT: codons: 1 - 261

There are no insertions or deletions

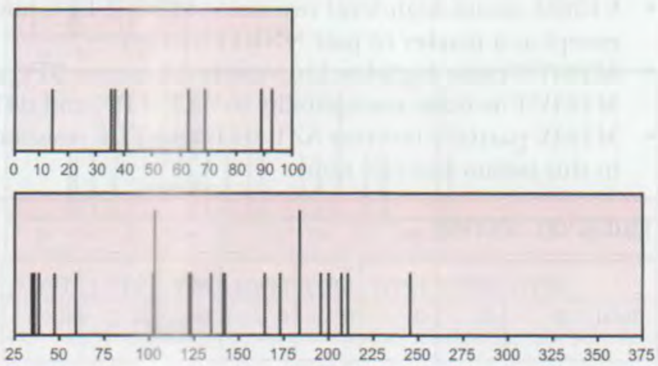
Subtype and percent similarity to closest reference isolate:

1. PR: C (93.6%)
2. RT: C (93.6%)

Sequence Quality Assessment

Gene	*QA Problem*	*Codons*
PR	Stop Codons, Frame Shifts:	*None*
PR	B,D,H,V,N:	*None*
PR	Unusual Residues:	*None*

Gene	*QA Problem*	*Codons*
RT	Stop Codons, Frame Shifts:	*None*
RT	B,D,H,V,N:	*None*
RT	Unusual Residues:	*None*



Blue lines indicate differences from consensus B; tall blue lines indicate sites associated with drug resistance.
Red lines indicate QA problems.

Drug Resistance Interpretation: PR

PI Major Resistance Mutations:	None
PI Minor Resistance Mutations:	None
Other Mutations:	I15V, M36I, N37S, R41K, L63S, H69K, L89M, I93L

Protease Inhibitors

Atazanavir/r (ATV/r)	Susceptible
Darunavir/r (DRV/r)	Susceptible
Fosamprenavir/r (FPV/r)	Susceptible
Indinavir/r (IDV/r)	Susceptible
Lopinavir/r (LPV/r)	Susceptible
Nelfinavir (NFV)	Susceptible
Saquinavir/r (SQV/r)	Susceptible
Tipranavir/r (TPV/r)	Susceptible

PR Comments

Special

- This sequence has 0 major TPV/r-resistance mutations, 1 minor TPV/r-resistance mutations (M36I), and 0 mutations associated with increased TPV/r responsiveness. RESIST study (Baxter J et al J Virology 2006 and Scherer J et al EACS 2007).

Other

- M36I is weakly associated with PI resistance in subtype B viruses when present with other mutations. However, M36I is the consensus amino acid in most non-B subtypes.
- L89M is a common polymorphism that is not associated with decreased PI susceptibility.
- I93L is a common polymorphism. It is the consensus residue in most subtypes. In subtype B, it is weakly associated with PI treatment.

Drug Resistance Interpretation: RT

NRTI Resistance Mutations:	M184V
NNRTI Resistance Mutations:	K103N
Other Mutations:	V35T, E36A, T39E, S48T, V60I, K102Q, K122E, D123S, I135V, I142V, T165I, K173A, G196R, T200E, Q207A, R211K, V245Q

Nucleoside RTI		Non-Nucleoside RTI	
Lamivudine (3TC)	High-level resistance	**Delavirdine (DLV)**	High-level resistance
Abacavir (ABC)	Potential low-level resistance	**Efavirenz (EFV)**	High-level resistance
Zidovudine (AZT)	Susceptible	**Etravirine (ETR)**	Low-level resistance
Stavudine (D4T)	Susceptible	**Nevirapine (NVP)**	High-level resistance
Didanosine (DDI)	Susceptible		
Emtricitabine (FTC)	High-level resistance		
Tenofovir (TDF)	Susceptible		

RT Comments

NRTI

- M184V/I cause high-level in vitro resistance to 3TC and FTC and low-level in vitro resistance to ddI and ABC. M184V/I increase susceptibility to AZT, TDF, and d4T.

NNRTI

- K103N causes high-level resistance to NVP, DLV, and EFV. By itself it has no effect on ETR susceptibility. However, it has a synergistic effect with L100I and possibly K101P on ETR susceptibility.

Mutation Scoring

PR	ATV/r	DRV/r	FPV/r	IDV/r	LPV/r	NFV	SQV/r	TPV/r
Total:	0	0	0	0	0	0	0	0

RT	3TC	ABC	AZT	D4T	DDI	FTC	TDF	DLV	EFV	ETR	NVP
K103N	-	-	-	-	-	-	-	60	60	10	60
M184V	60	12	-8	-5	5	60	-8	-	-	-	-
Total:	60	12	-8	-5	5	60	-8	60	60	10	60

The Team

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- Collaborators
- Acknowledgements

The Data

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- Database Statistics
- HIV Related Links
- Additional Resources

How would you now manage this patient?

Since there has been no development of major PI resistance mutations, it is likely that this child is still poorly adherent to medications. There has also been no evolution of TAMs. Immunologically, the child is stable and the CD4 count remains high. In this situation, adherence counseling should be intensified again. Since there are no major PI resistance mutations, LPV/r may be retained. Adherence should be addressed and the same regimen can be continued. Regular viral load follow-up will be helpful and if the child continues to have viral escape, access to repeat resistance testing would likewise be useful. If major PI resistance develops, new agents if available may be required.

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5.7

Laboratory Monitoring of HIV in Children

Janak A Patel

Introduction

HIV care of children and adults requires the monitoring of the disease progression as effectiveness of antiretroviral therapies (ART). Careful monitoring is critical for staging the disease, to initiate or to change ART, as well as to guide the prophylaxis for opportunistic infections. While the reduced cost of ART has lead to greatly expanded access in the recent years, the costs of laboratory monitoring have remained prohibitively high, thereby limiting the efforts at establishing comprehensive HIV care and services in resource-poor areas of the world.

In this chapter, the protocol for laboratory monitoring of HIV infected children in resource-poor as well as resource-rich settings is described. Monitoring of toxicities to ART is discussed elsewhere in this book. The guidelines for resource-poor settings are derived from the 2006 report of the National AIDS Control Organization (NACO), India[1] which are similar to those of the 2006 report of the World Health Organization (WHO).[2] The guidelines for the resource-rich settings are derived from the 2009 report by the Working Group on Antiretroviral Therapy and Medical Management of HIV infected Children, USA.[3] Table 5.7.1 provides the summary of the schedule for laboratory monitoring in HIV infected children in both resource-rich and resource-poor settings.

Immunologic Monitoring

Rationale for HIV Staging and Prognosis

Significant information has accumulated with regard to predicting the potential for disease progression in the

Table 5.7.1: Laboratory monitoring schedule for resource-rich and resource-poor settings

Test	*Resource-rich setting*	*Resource-poor setting*
CD4 count	- At initial diagnosis - Every 3-4 months - 1-2 months after starting ART[a] or changing ART - Clinical deterioration	- If limited resources permit, every 6 months
Total lymphocyte count[b]		- At initial diagnosis - Every 6 months in WHO clinical stage 2 disease
HIV viral load	- At initial diagnosis - Every 3-4 months - 1-2 months after starting ART or changing ART - Clinical deterioration	- If limited resources permit, every 6-12 months
HIV resistance test	- Prior to initiating ART - ART failure[c]	
Therapeutic drug monitoring	- Not routinely recommended - If resources permit, perform when clinical response lower than expected	

[a] ART - antiretroviral therapy
[b] Not useful in asymptomatic children or for monitoring ART efficacy
[c] Perform resistance test before stopping failing ART or within 4 weeks of stopping failing ART

pediatric HIV infected patient. Studies to date have demonstrated that the CD4+ cell count and/or CD4 percent is highly predictive of disease progression even in the young infant.[4-6] However, despite this large body of information, collected from both developed and developing countries, guidelines for treating young infants and very young children are not clear-cut because of the significant variability in disease outcome. Furthermore, the normal CD4 counts for various populations around the world have not been determined. Thus, there is some controversy among HIV clinicians as to when to begin therapy, even when these aforementioned factors are considered.

All studies to date have demonstrated that CD4+ cell count or CD4 percent has the strongest predictive value in predicting disease progression. Infants with CD4+ cell counts <1500 cells/ml and CD4 percent below 15 percent are more likely to develop opportunistic infections than are those with values that are higher.[4,7] Normal CD4+ levels can be as high as 2000-3000 cells/ml in infancy.[8] Based on these early studies, the Centers for Disease Control and Prevention (USA) developed a staging system that helps guide treatment (Table 5.7.2). However, for very young infants (younger than 1 year of age) these criteria have never been perfect; therefore, many experts have advocated for early treatment of all infants younger than 1 year of age. In children under age 5 years, the absolute CD4 count tends to vary more with age within an individual child than does CD4 percentage. Therefore, in HIV Infected children under age 5 years, CD4 percentage is preferred for monitoring immune status, whereas absolute CD4 count can be used in older children.[9,10] In HIV infected children, as in infected adults, the CD4 count and percentage decline as HIV infection progresses, and patients with lower CD4 values have a poorer prognosis than patients with higher values.

CD4 and HIV Viral Load Response to Treatment

The expected response to effective ART is restoration of the immune system. While immune reconstitution can be measured by a diverse number of laboratory assays, measurement of CD4 count is the most useful method. CD4 count recovery starts slowly and may continue for several months; on the other hand, HIV viral load declines more rapidly. However, rapid viral suppression is difficult in young children who typically have a high viral replication pattern. CD4 count may continue to improve or stabilize even with partial or failing ART, however, best results are seen if the ART is begun before severe deterioration of the immune system.

The long-term CD4 response to ART has been studied by many investigators. Resino et al studied 113 children who were treated with protease inhibitor-based highly active antiretroviral treatment (HAART) for at least six years.[11] An increase in CD4 cell counts and a decrease in viral loads occurred over the first two years of treatment. In the next four years, viral loads continued to fall, while CD4 cell counts had reached a plateau. Children starting

Table 5.7.2: Classification of immune suppression in children[1,7]

Classification of HIV associated immunodeficiency	*Age-related CD4 cell values*			
	<11 months (%)	*12-35 months (%)*	*36-59 months (%)*	*≥5 years (cells/mm³)*
Not significant (normal CD4 cells)	>35	>30	>25	>500
Mild	30-35	25-30	20-25	350-499
Advanced	25-30	20-25	15-20	200-349
Severe	<25 % or <1500 cells/mm³	<20 or <750 cells/mm³	<15 or <350 cells/mm³	<15% or <200 cells/mm³

Notes:
- CD4 is the best measurement for assessing immune deficiency
- CD4 should be used in conjuction with clinical assessment; however, CD4 allows an earlier detection of worsening of HIV disease as CD4 decline usually occurs prior to clincial progression
- CD4 monitoring can aid in the decision to initiate or switch ART
- Younger children normally have higher CD4 than older children and adults
- CD4 percent varies less in children <6 years old and is the preferred measurement
- At age ≥6 years, either CD4 percent and/or absolute CD4 count can be used
- The threshold CD4 cell levels for severe immuno-deficiency in children age 1 year and up, corresponds with a 12-month mortality risk of ≤5 percent. In children younger than 1 year and especially <6 months, CD4 is less predictive of mortality and there is high-risk for death even at high CD4 percent
- Normal CD4 count/percent in children are:
  <12 months: >1500 cells/mm³ (≥ 25%)
  1-5 years: >1000 cells/mm³ (≥ 25%)
  >6 years: >500 cells/mm³.

protease inhibitor treatment with low CD4 percent were less likely to exhibit immune restoration than those starting with higher CD4 levels. During the first two years of protease inhibitor-based treatment, children starting with CD4 percent below 25 percent showed a significant increase in CD4 percentage. However, CD4 levels failed to increase further over the next four years. HIV-1 infected children with CD4 percent of less than 5 percent at baseline experienced a slower restoration of CD4 percent than did HIV-1 infected children with baseline CD4 percent of 5 to 15 percent, and restoration of CD4 percent to a normal level could not be achieved during long-term HAART. These observations suggest that initiating HAART after severe immunosuppression has occurred is detrimental for the restoration of the CD4 cell count.

A meta-analysis of studies from resource-poor countries has shown that the CD4 and viral load response to treatment is comparable to those from resource-rich countries.[12] In this analysis, pooled estimates of the 12-month rate of virological suppression (HIV RNA <400 copies/ml) and increase in CD4 percent among children initiating antiretroviral therapies in African, Asian and Caribbean countries were studied. Out of a total of 5928 children who started ART, about 80 percent did not have viral load data and about 70 percent did not have CD4 percent data at 12 months. In a patient-level estimate after 12 months on ART, based on 1097 participants in 9 studies with complete data, the pooled proportion of children with virological suppression was 70 percent. Based on 1839 children in 12 studies with complete data, the pooled CD4 percent increase was 13.7 percent. This analysis shows that children in resource-poor settings achieve outcomes similar to those in wealthier countries despite the fact that they have more advanced disease on an average when starting treatment and are likely to receive less expensive older drugs, which may be less potent and less tolerable.

No alteration in therapy should be made as a result of a change in HIV copy number, or declining CD4 count or CD4 percent unless the change is confirmed by a second measurement.

Frequency of Monitoring in Resource-rich Settings

Once the diagnosis of HIV is confirmed, CD4 count and CD4 percent values should be obtained as soon as possible and every 3 to 4 months thereafter.[3] Increased frequency of evaluations may be needed for children with suspected clinical, immunologic, or virologic deterioration; to confirm an abnormal value; or when initiating or changing ART. Because young infants with HIV infection may have rapid disease progression, some experts monitor CD4 percentage more frequently (e.g. every 1-2 months) in untreated infants less than age 6-12 months.

Once the antiretroviral treatment is begun, CD4 measurements are obtained within 4-8 weeks and then every 3-4 months. Additional measurements may be needed with clinical deterioration. If treatment is changed, CD4 count should be repeated within 4-8 weeks.

Frequency of Monitoring in Resource-poor Settings

With resource limitations, the frequency of CD4 measurements may be reduced to every 6 months.[1,2] It may be repeated more frequently if clinically indicated due to clinical disease progression. When CD4 measurement is not available, the WHO guideline suggests using the total lymphocyte count (TLC) can be used in children with WHO clinical stage 2 disease.[2]

TLC = Percent lymphocytes x total white blood cell (WBC) count

The comparison of CD4 and TLC counts in severe immunodeficiency in children is shown in (Table 5.7.3). Unfortunately, TLC cannot be used in asymptomatic children or for monitoring ART efficacy in children. Figure 5.7.1 shows the 12-month mortality risk in children at selected thresholds for CD4 percent, absolute CD4 cell count and TLC.

Quantitative Virologic Monitoring

Rationale for Staging and Prognosis

HIV RNA level also has been found to be predicative of outcome, although it is a less sensitive measure of outcome than CD4 cell counts.[5,13] Those with HIV RNA levels >10,000 copies/ml are most likely to progress to AIDS or die. However, many infants with high HIV RNA levels do not progress, while others with much lower HIV RNA levels develop AIDS. Thus, it is really not possible to clearly determine who will or will not have rapid declines in CD4 cell count and/or rapidly progressive disease. This is because during primary viremia the majority of

Table 5.7.3: Diagnosing severe immunodeficiency using total lymphocyte count (TLC) in resource-poor settings or CD4 count in resource-rich settings[1,2]

Classification of HIV associated immunodeficiency	*Age-related TLC values (cells/mm³)*			
	<11 months	*12-35 months*	*36-59 months*	*≥5 years*
TLC	<4000	<3000	<2500	<2000
CD4 count	<1500	<750	<350	<200

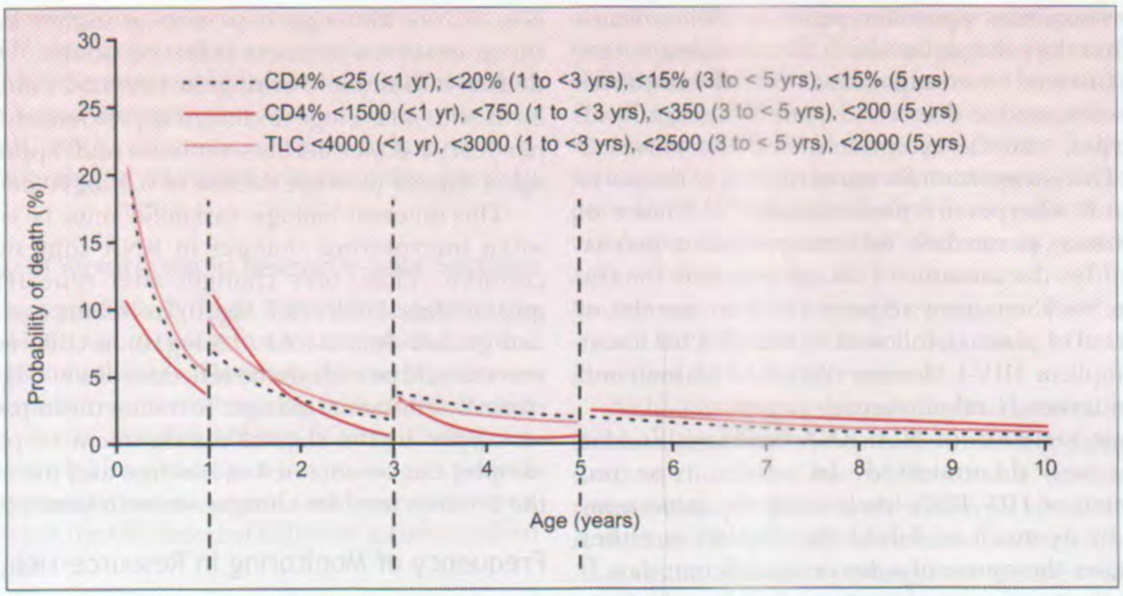


Fig. 5.7.1: 12-month mortality risk at selected thresholds for CD4%, absolute CD4 count and total lymphocyte count (TLC), by age[2]

neonates can be found to have HIV RNA levels that are >100,000 copies/ml, if they are tested frequently in the first 8 weeks of life and are untreated or minimally treated.

The HIV Prognostic Markers Collaborative Study Group published the 12-month risk of disease progression in a large meta-analysis that used CD4+ cell count and HIV RNA data from almost 4000 children from cohorts around the world.[5] This study showed that the risk for disease progression increased linearly with increasing levels of HIV RNA, and a more sharp increase in risk was observed for infants with viral load > 100,000 copies/ml. As a result of this study, a website was created on which one can enter CD4+ cell count or HIV RNA and age to determine the short-term risk of progression to AIDS or death if untreated with antiretroviral therapy. *The website is http://www.ctu.mrc.ac.uk/penta/hppmcs/calcprob.htm.*

Despite data indicating that high plasma HIV RNA concentrations are associated with disease progression, the predictive value of specific HIV RNA concentrations for disease progression and death for an individual child is moderate.[14] In both HIV infected children and adults, CD4 percentage or count and HIV RNA copy number are independent predictors of disease progression and mortality risk, and use of the two markers together more accurately defines prognosis.[14-17]

Methodological Considerations in Interpretation and Comparability of HIV RNA Assays

Several different methods can be used for quantifying HIV RNA, each with different levels of sensitivity. Although the results of the assays are correlated, the absolute HIV RNA copy number obtained from a single specimen tested by two different assays can differ by 2-fold (0.3 log10) or more.[18]

There are currently five FDA-approved (USA) viral load assays:

- **HIV-1 reverse transcriptase (RT) quantitative PCR assays**
  - The Amplicor HIV-1 Monitor Test, version 1.5 (Roche Diagnostics); lower limit of detection differs between the "ultrasensitive" assay (<50 copies/mL) and "regular sensitivity" assay (<400 copies/mL)
  - The AmpliPrep/TaqMan HIV-1 Test (Roche Diagnostics)
  - The Real Time HIV-1 Assay (Abbott Molecular Incorporated)
- **HIV-1 nucleic acid sequence-based amplification test** (NucliSens HIV-1 QT, bioMerieux)
- **HIV-1 *in vitro* signal amplification, branched chain nucleic acid probe assay** (bDNA) (Versant HIV-1 RNA 3.0 Assay, Bayer).

The lower limit of detection for the assays differs (<40 copies/ml for Abbot Real Time HIV-1 Test, <48 copies/ml for the AmpliPrep/TaqMan HIV-1 Test, <50 copies/ml for the Amplicor HIV-1 Monitor Test, <80 copies/ml for the NucliSens HIV-1 QT assay, and <75 copies/ml for the Versant assay). Because of the variability of assay techniques and quantitative HIV RNA measurements between the three assays, a single HIV RNA assay method should be used consistently for monitoring an individual patient. A key goal of therapy is to lower the viral load below the limit of detection of the chosen assay.

The predominant virus subtype in the United States is B, which is the subtype for which all initial assays were targeted. Current kit configurations for all companies have been designed to detect and quantify essentially all viral subtypes, with the exception of the uncommon O subtypes. This is important for many regions of the world where non-B subtypes are predominant.[19-21] Choice of HIV RNA assay, particularly for young children, may be influenced by the amount of blood required for the assay. The NucliSens assay requires the least amount of blood (100 µl of plasma), followed by the RT PCR assays such as Amplicor HIV-1 Monitor (200 µl of plasma) and the Versant assays (1 ml of plasma).

Biologic variation in HIV RNA levels within one person is well documented. In adults, repeated measurement of HIV RNA levels using the same assay can vary by as much as 3-fold (0.5 log10) in either direction over the course of a day or on different days.[22] This biologic variation may be greater in infected infants and young children. In children with perinatally acquired HIV infection, RNA copy number slowly declines even without therapy during the first several years after birth (Fig. 5.7.2), although it persists at higher levels than those observed in most infected adults.[14,23,24] This decline is most rapid during the first 12-24 months after birth, with an average decline of approximately 0.6 log10 per year; a slower decline continues until approximately age 4-5 years (average decline of 0.3 log10 per year).

This inherent biologic variability must be considered when interpreting changes in RNA copy number in children. Thus, only changes after repeated testing greater than 5-fold (0.7 log10) in infants age <2 years and greater than 3-fold (0.5 log10) in children age ≥ 2 years should be considered reflective of a biologically and clinically substantial change. To reduce the impact of assay variability in the clinical management of patients, 2 samples can be obtained at baseline and the average of the 2 values used for comparison with future tests.

Frequency of Monitoring in Resource-rich Settings

HIV RNA copy number should be assessed as soon as possible after a child has a positive virologic test for HIV and every 3-4 months thereafter; increased frequency of evaluations may be needed for children experiencing

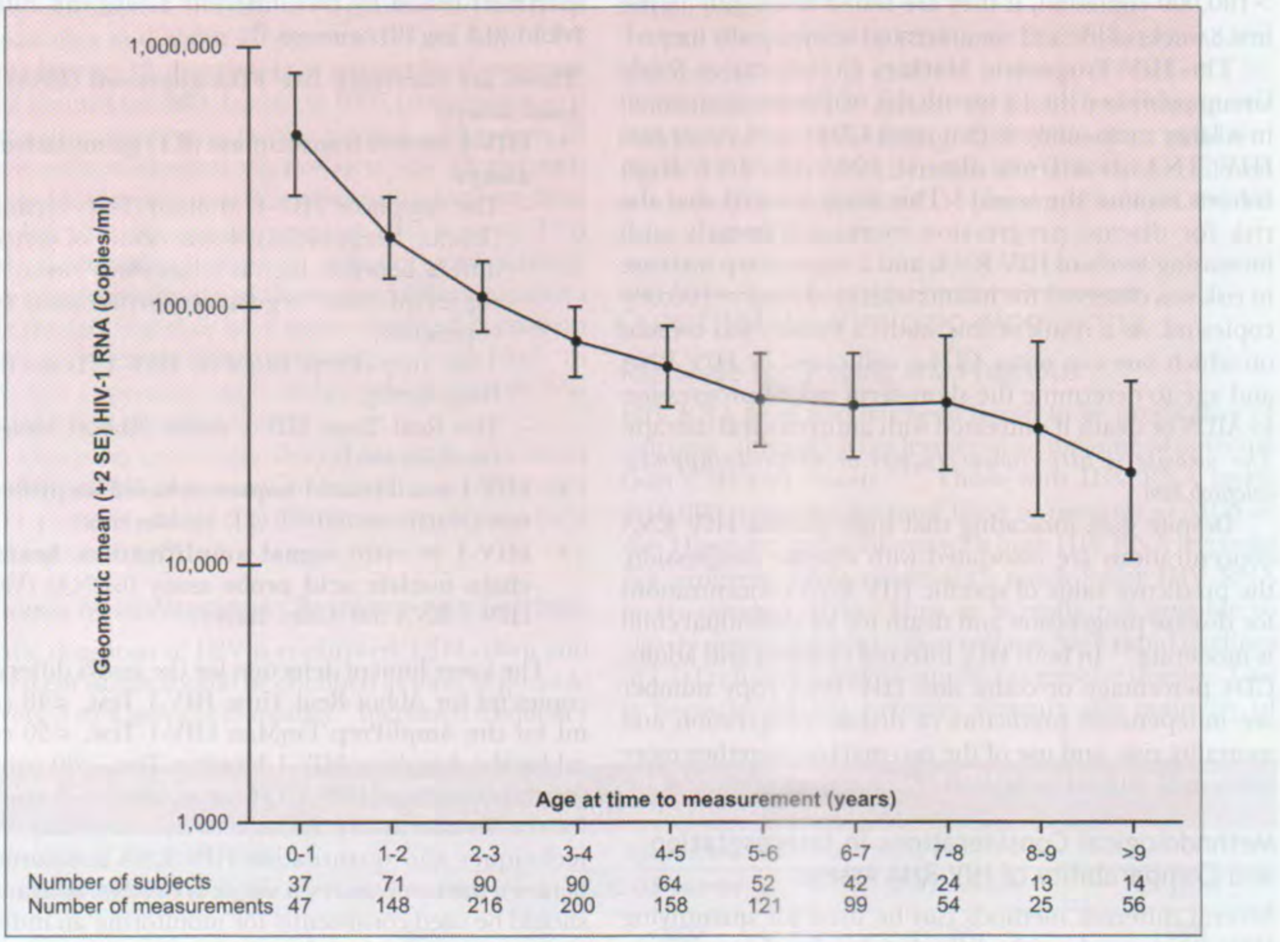


Fig. 5.7.2:. Mean (± 2 SE) serum HIV-1 RNA levels by age at time of measurement[6]

virologic, immunologic, or clinical deterioration; to confirm an abnormal value; or when initiating or changing ART. Because young infants with HIV infection may have rapid disease progression, some experts monitor HIV RNA concentration more frequently (e.g. every 1-2 months) in untreated infants under age 6-12 months.

Frequency of Monitoring in Resource-poor Settings

Due to the tremendously high costs of the assays, the NACO and WHO guidelines do not recommend routine testing of HIV viral loads. However, if limited resources permit, even less frequent monitoring once or twice yearly may help assist in identifying failing therapies. Continuation of failing therapies for prolonged periods allows for accumulation of several resistance mutations, which increases the likelihood of failure of second or third line therapies.

Monitoring HIV Drug-Resistance

Mutations in HIV RNA readily arise during viral replication because HIV reverse transcriptase is a highly error-prone enzyme. Consequently, ongoing replication in the presence of ART readily and progressively selects for strains of HIV with mutations that confer drug resistance. Resistance assays have been extremely valuable in selecting the most appropriate ART which produces the most durable response and lead to reduced morbidity and mortality. However, in resource-poor settings, the extremely high-costs of the resistance assays make them impractical for routine use in clinical care of HIV infected children. Therefore, the NACO and WHO guidelines have not incorporated resistance testing in the treatment guidelines.

Use of Resistance Assays in Determining Initial Treatment

Mother-to-child transmission and horizontal transmission of drug-resistant HIV strains have been well documented and are associated with suboptimal virologic response to initial antiretroviral therapy.[25,26] Drug-resistant variants of HIV may persist for months after birth in infected infants and impair the response to antiretroviral therapy.[27,28] Consequently, antiretroviral drug-resistance testing is recommended prior to initiation of therapy in all treatment-naïve children.

Use of Resistance Assays in the Event of Virologic Failure

Several studies have been performed in adults indicating that early virologic responses to salvage regimens were improved when results of resistance testing were available to guide changes in therapy, compared with responses observed when changes in therapy were guided only by clinical judgement.[29,30] Although not yet confirmed in children, resistance testing appears to be a useful tool in selecting active drugs when changing antiretroviral regimens in cases of virologic failure.[31] Resistance testing also can help guide treatment decisions for patients with suboptimal viral load reduction because virologic failure in the setting of combination antiretroviral therapy may be associated with resistance to only one component of the regimen. Poor adherence should be suspected when no evidence of resistance is identified to a failing regimen.

Although drug resistance may be detected in infants, children, and adults who are not receiving therapy at the time of the assay, loss of detectable resistance and reversion to predominantly wild-type virus often occur in the first 4-6 weeks after antiretroviral drugs are stopped. As a result, resistance testing is of greatest value when performed before or within 4 weeks after drugs are discontinued. The absence of detectable resistance to a drug at the time of testing does not ensure that its future use will be successful[24] especially if it shares cross-resistance with drugs previously used; it may be prudent to repeat resistance testing if an incomplete virological response to a new treatment regimen is an individual with prior treatment failure(s).

Resistance Assays

Drug-resistance detection methods vary depending on the class of antiretroviral agents. Both genotypic assays and phenotypic assays are used to detect the presence of virus that is resistant to inhibitors of the HIV reverse transcriptase and protease enzymes. Relevant to India is that experience is limited with the use of commercially available genotypic and phenotypic assays in the evaluation of drug-resistance in patients infected with non-B subtypes of HIV. [32]

The International AIDS Society-USA (IAS-USA), the Los Alamos HIV Drug-Resistance Database, and the Stanford University HIV Drug-Resistance Database maintain lists of significant resistance-associated mutations relevant to currently available antiretroviral drugs *(see http://www.iasusa.org/resistance_mutations, http://hiv-web.lanl.gov, or http://hivdb.stanford.edu)*. A variety of online tools that take into account the ability of some mutations selected by one drug to cause partial or full cross-resistance with other drugs are now available to assist the provider in interpreting genotypic test results. Although the response to antiretroviral therapy in children and adolescents is not always predicted by the results of genotypic resistance assays, clinical trials in adults have demonstrated the benefit of resistance testing combined with consultation with specialists in HIV drug-

resistance in improving virologic outcomes.[29,30] Given the potential complexity of interpretation of genotypic resistance, it is recommended that clinicians consult with a specialist in pediatric HIV infection for assistance in the interpretation of genotypic results and design of an optimal new regimen.

Limitations of Current Resistance Assays

Limitations of the genotypic, phenotypic, and phenotype-prediction assay approaches include lack of uniform quality assurance testing and high cost. In addition, drug-resistant viruses that constitute <10-20 percent of the circulating virus population may not be detected by any of the currently available assays. Consequently, a review of the past use of antiretroviral agents is important in making decisions regarding the choice of new agents for patients with virologic failure.

Therapeutic Drug Monitoring (TDM)

TDM is the term used to describe the use of plasma drug concentration measurements as part of a strategy to optimize drug dosing to minimize toxicity and maximize treatment benefit. TDM can be considered for use in ART monitoring: (i) there is high interpatient variability in antiretroviral exposure (plasma drug concentrations) using standard recommended doses; (ii) low drug exposure can lead to suboptimal virologic response to therapy; and (iii) high plasma concentrations can be associated with increased-risk of drug toxicity.

Developmental pharmacokinetic differences contribute to greater variability in pediatric patients and a greater frequency of suboptimal antiretroviral exposure than in adults.[33] Pediatric dosing is designed to mimic adult exposure and rarely reflects the maximum tolerated antiretroviral drug dose. Even when using dose recommendations from published pediatric guidelines, children frequently receive inadequate antiretroviral doses.[34]

TDM may be considered in the following circumstances where it is potentially useful: (i) patients in whom clinical response is different from that expected; (ii) treatment-experienced patients infected with virus with reduced drug susceptibility, where a comparison of the drug susceptibility of the virus and the achieved drug concentrations may be useful; (iii) patients with potential drug administration difficulties, including suboptimal dietary intake, malabsorption, incorrect dose, caregiver measuring errors, or adherence concerns; and (iv) drug or food interactions, including alteration of drug formulations by crushing or mixing with various foods and liquids.

The extremely high costs as well as lack of availability of these assays in commercial settings make the use of TDM in resource-poor settings impractical. Indeed, the NACO and WHO guidelines do not incorporate TDM in routine clinical care. Even in resource-rich settings, TDM use is highly limited.

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5.8

Antiretroviral Treatment Toxicities in Children

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Introduction

In the last years, major advances have been made in the prevention and treatment of HIV infection. Because of that, a dramatic decline in morbidity and mortality has been observed. HIV infection has become a chronic disease facing new challenges. The improvement in the prognosis of HIV infection with HAART certainly promises a longer lifespan for children but also an increased exposure to potential toxic drugs.

Toxicity is one the greatest barrier to highly active antiretroviral therapy (HAART) and the associated metabolic complications seriously compromise treatment's success. The increasing prevalence of metabolic abnormalities observed in children treated with HAART is of major concern.[1] Although there are fewer data on toxicity than in adults, the complete spectrum of metabolic complications observed in adults has been reported in children.

Definition of Toxicity and Classification

Toxicity may be **drug-specific**, **class-specific** or a possible **cofactor** involved in a complex generalized metabolic disarrangement. Single-agent toxicities usually manifest early and reverse after withdrawal of the specific drug (Appendix 5.8.1). Class toxicities generally are more subtle, manifest slowly and after longer periods of exposure. The combined toxic effects of HAART along with the damage caused by the virus itself and the associated immunological changes, possibly stem for the vast array of metabolic disorders that may occur. NRTI are toxic for the mitochondrial DNA and are the main responsible agents for hyperlactatemia and peripheral lipoatrophy. NNRTI may cause liver toxicity and hyperlipidemia. Most PIs are associated with hyperlipidemia, insulin resistance and may contribute in the development of lipohypertrophy. In this chapter we are going to talk about metabolic toxicity associated with the use of antiretrovirals (ARVs):

1. Mitochondrial toxicity.
2. Lipodystrophy syndrome (LDS).
3. Dyslipidemias.
4. Insulin resistance.
5. Disorders of bone metabolism.
6. Metabolic considerations before beginning ARV therapy.
7. Risk factors for cardiovascular disease.

Mitochondrial Toxicity

NRTI induced inhibition of DNA-polymerase gamma lead to mtDNA depletion and subsequent decrease in mtDNA-encoded proteins and mitochondrial dysfunction. In adults and children treated with NRTI for longer than 6 months, asymptomatic hyperlactatemia is common. Few studies have assessed the prevalence of hyperlactatemia in HIV infected children. Difficulties in determining venous lactate in optimal conditions result in lack of specificity. Even true hyperlactatemia is usually asymptomatic and may be transient. The prevalence of hyperlactatemia in HIV infected children treated with NRTI ranges between 6 and 36 percent.[2,3] In contrast, the incidence of symptomatic hyperlactatemia is low. Large prospective studies in adults have estimated an incidence of symptomatic hyperlactatemia of 0.8-1.7 per 1000-patient-years. Severe lactic acidosis is the most feared spectrum of the toxicity attributed to NRTI as it is associated with a high mortality. Isolated case reports of severe lactic acidosis have been reported in HIV infected children.[4] The predictive value of lactate determinations is low, suggesting that routine lactate should not be checked in clinical practice in the absence of symptoms. Nevertheless a high index of suspicion for symptomatic

hyperlactatemia is necessary because early symptoms are non-specific (fatigue, weakness, myalgias, gastrointestinal, respiratory or neurological symptoms, hepatic steatosis, pancreatitis, etc.) (Table 5.8.1).

If symptomatic hyperlactatemia is diagnosed, withdrawal of all antiretrovirals (ARV) is necessary and supportive treatment and multivitamins should be considered. Following recovery, administration of an NRTI-sparing regimen is the safest option, although an NRTI with less potential mitochondrial toxicity may be cautiously introduced, such as abacavir (ABC), lamivudine (3TC), emtricitabine (FTC) or tenofovir (TDF) and avoiding stavudine (d4T) and didinosine (ddI).[1]

A special situation occurs in children born to HIV infected mothers exposed to NRTI *in utero* in whom the prevalence of transient hyperlactatemia is very high, suggesting reversible mitochondrial dysfunction.[5] Although the great majority of children are asymptomatic, these infants have a slightly higher-risk of mitochondrial disorders including severe neurological dysfunction.[6] Despite some scarce disturbing reports, the very low-risk is outweighed by the success of NRTI in preventing vertical transmission. The usefulness of lactate determination in exposed noninfected children during the first months of life, is questionable and it is usually not done in clinical practice.

Lipodystrophy Syndrome (LDS)

The LDS encompasses changes in fat distribution typically manifesting as lipoatrophy, with or without central adiposity, and it is frequently associated with alterations in lipid regulation and glucose homeostasis. Despite difficulties in assessment and a lack of a standardized definition, fat maldistribution is increasingly recognized in children and is of great concern, not only because of its potential future metabolic consequences but also by the impact that body changes may have on self-image in children and adolescents and subsequent stigmatization resulting in bad adherence and treatment failure. Although affected children exhibit different patterns and severity of fat maldistribution, lipoatrophy is more specific to HIV infection.[1]

Current cross-sectional studies estimate that the prevalence of LDS is between 18-38 percent as assessed on clinical grounds and anthropometric measurements.[8-12] Clinical recognition of LDS underestimates the true prevalence of the syndrome. Several studies have observed abnormalities in fat distribution by DEXA before clinical signs are recognized.[13] Various objective techniques to assess the changes in fat distribution have been used. DEXA provides accurate information about subcutaneous fat, whereas CT or MRI scanning are more reliable in discriminating between subcutaneous fat stores and visceral fat.[1]

Table 5.8.1: Diagnosis and management of lactic acidosis[7]

- Abnormal values of serum lactate must be confirmed with second determination and include serum bicarbonate, anion gap, amylase, lipase, arterial blood gas and sometimes imaging studies to evaluate liver or pancreas
- **1st scenario:** Lactate < 2 mmol/l and normal bicarbonate: Continue ARV
- **2nd scenario:** Lactate 2.1-5 mmol/l:
  - **1st option:** Continue ARV if normal bicarbonate but close monitoring of symptoms is recommended
  - **2nd option:** Stop HAART until additional diagnoses are confirmed
- **3rd scenario:** Lactate >5 mmol/l and symptomatic, or lactate >10 mmol/l regardless of symptoms: stop HAART and start supportive therapy [IV fluids, oxygen, sedation, and respiratory support; and consider: bicarbonate infusion, thiamine (vitamin B1) and riboflavin (vitamin B2), oral antioxidants (e.g. L-carnitine, coenzyme Q, vitamin C)]
- After resolution of clinical and laboratory abnormalities, ARV therapy can be started avoiding NRTI or using some NRTIs with less mitochondrial toxicity (ABC or TDF and with caution ZDV or 3TC). It is important to monitor lactate and symptoms after resuming ARV treatment for at least 3 months.

(TDF: It is not licensed for children <18-years).

The Patterns of LDS[11,12]

- ***Peripheral lipoatrophy (Lipoatrophy):*** Decreased subcutaneous fat, most prominent in the face, and limbs, and manifested as sunken cheeks and eyes, prominent zygomatic arch, as well as skinny, prominent veins, muscularity and bones in arms and legs.
- ***Central obesity (Lipohypertrophy):*** Central fat accumulation and manifested by increased abdominal girth and fat accumulation in the dorsocervix region. Frequently both patterns coexist.
- ***Mixed patterns.***

Risk Factors that may be Involved:

- ***ARV:*** Longitudinal studies have reported an increase in peripheral fat loss and central fat accumulation by sequential imaging techniques with regard to baseline in children who continued the same antiretroviral regimen, suggesting that changes in fat distribution are progressive and related to duration of HAART.[13] Peripheral lipoatrophy is linked to d4T use, especially if combined with ddI. Some but not all studies have found an association between PI treatment and the presence of fat maldistribution. In most adult studies an association between central fat accumulation and PI-exposure have been shown.[1]
- ***Sex:*** The syndrome appears to be more common in females and increases with age.

- ***Tanner stage:*** Visceral fat accumulation is greater in pubertal compared with prepubertal children.
- ***Disease stage:*** Children with lipoatrophy have a more advanced disease and lower BMI.
- ***Visceral fat*** has been associated with increased cardiovascular risk due to its association with insulin resistance and dyslipidemia.

Management of LDS (Table 5.8.2)

It is not known whether fat distribution abnormalities are reversible. In lipoatrophic adults, switching from d4T to ABC or TDF led to mild but significant increases in peripheral fat at 24-96 weeks measured by DEXA, but not clinically observed, suggesting that clinical improvement may take years to be apparent. In contrast, switching the PI by NNRTI or abacavir has lead to improvement in dyslipidemia and insulin resistance but not significant changes in fat redistribution have been observed.[14]

Another approach implies investigational strategies. In a small preliminary study in adolescents with fat accumulation, rhGH has shown promising results with improvement in intra-abdominal fat at 24 weeks.[15] So, GH-levels could be important. In a multivariate analysis, children with lower baseline IGF-1 and IGFBP-3 showed lower mean weight, height and mid-arm muscle circumference and those who normalized IGF-1 after initiation of ARV had greater increase in muscle mass. Other investigational treatments are metformin, thiazolidinediones or testosterone.[16]

Although adult studies have not demonstrated that treatment interruptions result in improvement of fat maldistribution, no specific studies have been done. Studies on specific drug substitution and discontinuation of HAART are needed in children.

Finally, surgery could be considered in older adolescents with disfiguring fat maldistributions or psychological problems after considering medical treatment options (discontinuing ARVs implicated and using other drugs with better profile, simplification strategies, exercise, diet, etc). Despite the potential for recurrence, surgical management of lipodystrophy is efficacious mainly in lipohypertrophy.[17]

Table 5.8.2: Diagnosis and management of LDS

Diagnosis: **Clinical examination plus objective measurements:**

- ***Anthropometric measurements:*** Skin folds (subcutaneous fat), Body Mass Index (BMI); waist and hip circumference (correlated with visceral fat).
- ***Bioelectrical impedance:*** To asses lean body mass and total body fat but not fat distribution.
- ***Dual energy X-ray absorptiometry (DEXA):*** To asses fat distribution (arm, leg and trunk)
- ***Abdominal computed tomography or magnetic resonance imaging (MRI):*** To discriminate between subcutaneous and visceral fat

Management:

- **Drug substitutions:**
  Lipoatrophy: Avoid d4T, ddI. Use if possible: ABC, TDF, ZDV
  Lipohypertrophy: Avoid PIs (mainly indinavir). Use if possible efavirenz or nevirapine.
- **Investigational therapies:**
  Lipohypertrophy: GH (monitor glucose)
- **Treatment interruption:** close monitor is needed because the disease can progress
- **Surgery:** Consider after medical options. Only in adolescents or young adults who have reached Tanner V (complete puberty).
  Facial lipoatrophy: Fat autotransplantation, malar implants
  Lipohypertrophy: Lipectomy[17]

Dyslipidemias

Many other metabolic abnormalities are increasingly being reported in children. The relationship among each other and with LDS is not known, although they may frequently coexist.[12] Dyslipidemias are more common in patients with LDS. PIs are the drugs most commonly involved in dyslipidemias, although it may occur with PI-sparing regimens.[18] Nevertheless, before ARVs were available, some lipid abnormalities were observed including low levels of HDL and elevated TG. The reported prevalence has been variable and the definition of hypercholesterolaemia and hypertrigliceridemia have also varied among studies.[12,18,19] In children, hypercholesterolemia appears to be more common than hypertriglyceridemia (Table 5.8.3 and Table 5.8.4).[12] In the largest published series of lipid assessment in pediatrics, of nearly 2000 HIV infected children studied, 13 percent had cholesterol levels higher than the 95th percentile. After multivariate analysis, PI use, concomitant NNRTI use, and self-reported adherence were independent risk factors for hypercholesterolemia. Dual PI-regimens and ritonavir boosted PIs have been most associated with abnormal blood cholesterol and triglycerides.[18] PI-containing regimens are also associated in children with increases in LDL and the ratio LDL/HDL, a better marker of atherogenic risk.[1] All children on ritonavir boosted PIs including lopinavir/r should have

Table 5.8.3: Hypercholesterolemia and hypertriglyceridemia (American Academy of Pediatrics classification, 1998)[28]

- In all patients check fasting lipid profile before ARV initiation and every 3-6 months thereafter
- Ensure fasting of at least 8 hours before collection of samples for measurements of triglycerides (TG), total cholesterol (cho), LDL-cho, HDL-cho.
- Avoid PIs and d4T. Use if possible ABC, TDF
- Goal: LDL <130 mg/dL, TG <150 mg/dl (Triglyceride levels <200 mg/dL are considered acceptable).

Table 5.8.4: Hypercholesterolemia (NCEP classifications for children and adolescents, American Academy of Pediatrics classification,1998)

Hypercholesterolemia NCEP classifications	*Total cholesterol*	*LDL cholesterol*
High	>200 mg/dL	>130 mg/dL
Borderline	170-179 mg/dL	110-129 mg/dL
Acceptable	<170 mg/dL	<110 mg/dL

fasting blood lipids measured at least every year.[20,21] Simplification strategies like switching from the PI to a NNRTI or ABC have been associated with a decrease in total and LDL-cholesterol and are increasingly being used in adults.[22] In children there is a successful, albeit limited experience in lowering cholesterolemia and LDL-cholesterol by switching from the PI to efavirenz,[23] nevirapine[24] and in selected patients, also to ABC.[25] There is very limited experience of statins in children. Although longitudinal data for the consequences of dyslipidemia in pediatric population are not available, we can hypothesize that these patients could develop a premature atherosclerotic disease because they have levels of cholesterol similar to those seen in patients heterozygous for familial hypercholesterolemia.[26] So, the management of lipid disorders is important although, sometimes it is not easy. The first recommendation is diet and exercise (Table 5.8.5) and another strategy for managing dyslipidemia is to switch from a PI to NNRTI or ABC and use d4T-sparing regimens. If this intervention is not enough, lipid lowering agent could be used with caution because some of them are metabolized by the P450 enzyme as well as PIs or NNRTI and therefore serum concentrations of statins can be affected leading to adverse events (PIs inhibit and NNRTIs induce hepatic metabolism). Statins can be used in children older than 10 years with LDL > 190 mg/dl or 160 mg/dl if they have family history of coronary artery disease and only after 6 to 12 months of diet and exercise without any improvement in levels of cholesterol. Dose of statins can be increased slowly and always with caution. Finally, few data exist about statins use even in non HIV infected children. So, children who start this medication must be carefully monitored.[27] In conclusion, lipid and metabolic abnormalities seen in HIV positive patients emphasize the need for close monitoring, choosing metabolically-friendly ARV regimens when possible, and initiating lipid drug therapy when appropriate.

Insulin Resistance

Derangements in glucose homeostasis are also common in patients treated with HAART. It is unclear whether insulin resistance is associated with growth delay in HIV infection or with atherosclerosis but seems that may be associated with lipodystrophy.

Table 5.8.5: Management of hypercholestrolemia and hypertriglyceridemia

If LDL >130 mg/dl

1st step (6-12months):

- Diet and exercise.
- Consider changes in ARV therapy: Avoid PIs or use some with better lipid profile like atazanavir or use efavirenz or nevirapine instead of PIs if possible
- Simplification strategies in patients with stable immuno-virological situation and undetectable viral load for at least 6 months could be considered. Switch from d4T to ZDV, ABC or TDF or from PI to ABC if possible (consider resistance mutations, previous treatment, adherence...)

2nd step: If inadequate response, consider lipid lowering drugs in children older than 10 years with LDL > 190 mg/Dl or 160 mg/Dl if they have family history of coronary artery disease and only after 6 to 12 months of diet and exercise without any improvement.

Lipid lowering drugs for treatment of elevated cholesterol:

Statins (HMG-CoA reductase inhibitors: Pravastatin and atorvastatin):

- Approved for children >10 years of age; Initial dose 10 mg/qd (start at low dose, titrate slowly)
- Caution with drug-drug interactions (PIs inhibit and NNRTIs induce hepatic metabolism, so, statins´ level could be modified)
- Adverse effects: Liver and muscle toxicity. Monitor creatine kinase. Avoid in patients who are or may become pregnant

Ezetimibe: Inhibits intestinal absorption of cholesterol

- Limited pediatric information; appears to be safe and effective in HIV-uninfected children >10 years of age

Combine Statins and Ezetimibe

Not recommended: Acid-binding resins

Hypertryglyceridemia

If TG >500 mg/dl, immediate treatment indicated

Fibrates (gemfibrozil and fenofibrate)

- Can interact with statins and cause myositis, rhabdomyolysis, bone marrow suppression
- Less efficacy in dyslipidemia due to PI
- Avoid statins + fibrates (ezetimibe + fibrates can be an alternative in hypertriglyceridemia plus hypercholesterolemia)

Although fasting glucose remain normal in most adults, impaired glucose tolerance and hyperinsulinemia are not uncommon in PI-treated patients, and the incidence of diabetes mellitus is increased in HIV infected adults treated with PI compared with untreated HIV-patients.[21,29] Although, the PIs have been most extensively studied in adults, the cumulative exposure to NRTI may also play a role in insulin resistance.[30] The lack of a standardized definition of insulin resistance has led to inconsistencies in reporting its prevalence. PI-treated children frequently have fasting hyperinsulinemia, particularly adolescents and children with LDS.[10] Due to the lack of feasibility of the gold standard for insulin resistance, the euglycemic clamp and other diagnostic strategies with variable correlation, have been used. Most

available laboratory methods are insufficiently sensitive to detect early disturbances in glucose homeostasis. Insulin sensitivity is linked to many factors including age, puberty, diet, etc. By using the insulin-modified frequent-sampling iv glucose tolerance test, a lower insulin sensitivity index in PI-treated than non-PI treated HIV infected children has been shown, suggesting a certain degree of insulin resistance.[31] Furthermore, there is a significant correlation between insulin resistance, hyperlipidemia and increased visceral fat content as determined by abdominal CT, suggesting that PI-containing HAART regimens might be associated with the emergence of early features of a metabolic syndrome-like phenotype and may increase the cardiovascular risk. The future consequences of hyperinsulinemia and its management in children are unknown. Pubertal children with lipohypertrophy may have an increased risk and monitoring of insulin and glucose homeostasis should be considered.[31] The first approach is dietary modification, weight control and aerobic exercise although these strategies have more impact in dyslipidemia. Switch strategies with NNRTI or abacavir substitution for the PI has been associated in some studies with short-term improvements in adults and should be considered in this setting.[32] The thiazolidenediones have shown efficacy in adults with type II diabetes but there is no experience in children.

Metformin is not licensed in children under 10 year old and lactic acidosis and hepatic damage have been reported in HIV infected patients, so must be used with caution.

Finally, there are scant data on the effect of HAART on glucose metabolism in pregnant HIV infected women. PI based regimens have been associated with the development of gestational diabetes in some studies.[33] Therefore, glucose levels must be monitored in women who receive PIs during pregnancy, mainly if they have other risk factors (older age, family history of diabetes, gestational diabetes in a previous pregnancy) (Table 5.8.6).

Table 5.8.6: Definitions and management

Normal value:

Fasting glucose < 110 mg/dl

Oral glucose tolerance test: glucose at 2nd hour < 140 mg/dl

Impaired glucose tolerance:

Fasting glucose: 110 to 126 mg/dl

Oral glucose tolerance test: Glucose at 2nd hour >140 to 200 mg/dl

Diabetes mellitus:

Fasting glucose >126 mg/dL or random glucose >200 mg/dl

Oral glucose tolerance test: Glucose at 2nd hour > 200 mg/dl

Gestational diabetes mellitus (GDM):

O´Sullivan test might to be performed in all HIV infected women at 24-26 weeks. This test is considered abnormal when the value of plasma glucose 1 hour after 50 g of oral glucose administration is ≥ 140 mg/dl. When this test is abnormal, an oral glucose tolerance test is performed at 28-30 weeks. After 100 g of oral glucose dose, the test is considered abnormal when ≥ 2 values of plasma glucose are higher than these values: Fasting glucose ≥ 105 mg/dl, or plasma glucose 1 hour after glucose load ≥ 190 mg/dL, or plasma glucose 2 hours after glucose load ≥ 165 mg/dl, or plasma glucose 3 hours after glucose load ≥ 145 mg/dl. When two values are abnormal, the diagnosis of GDM is established.

Homeostasis model assessment of insulin resistance (HOMA): insulin (µg/ml) × glucose (mmol/l)/22.5

Normal value in adults: 1.21-1.45

Abnormal >2 (not validated in HIV infected patients)

Measurements of **insulin, C-peptide**

Management:

- Patients must be aware of symptoms of diabetes.
- Recommend diet and aerobic exercise.
- Determine fasting glucose in patients with risk factors for diabetes (family history of diabetes, lipodystrophy, etc).
- If random glucose is >140 mg/dl, check fasting glucose.
- Consider switching from PI to NNRTI.
- Sometimes, oral medications or insulin could be required.

Disorders of Bone Metabolism

There have been increasing reports of osteonecrosis and abnormalities of bone mineral metabolism in adult patients on HAART. Osteonecrosis usually results from circulatory insufficiency, and the areas most often involved are the femoral and humeral heads. A large cross-sectional study using MRI detected avascular necrosis of the hip in 4 percent in adults, even before clinical symptoms developed.[34] In children, avascular necrosis has been seldom reported but may be difficult to diagnose early and result in severe sequelae. A large case-control study has suggested that Legg-Calve-Perthes disease is 9 fold more frequent in HIV infected children than in the general population.[35]

The incidence of osteopenia and osteoporosis is increased in patients treated with HAART, although the association with PI is not clear as initially suggested.[34] The pathogenesis is not obvious, although decreased bone mineral content seems to be the consequence of an insufficiency in mineral bone metabolism that in turn might develop as a result of increased bone turnover, with predominant bone reabsorption. Osteopenia may be induced by multiple factors including HAART, and the duration of infection. There is no consensus on the definition of osteopenia and osteoporosis in children. There are scarce standards for age and sex of bone mineral mass in children. DEXA is the most common and reliable image technique used in adults. Nevertheless, its use in children is cumbersome as the only available z-score is in the lumbar spine and no adjustment is made by vertebral size. Due to HIV infected children showing lower weight and height scores than general population, results obtained by DEXA could overestimate the prevalence of bone abnormalities.[3] Scan is more accurate because it can perform a volumetric

analysis but its use is limited. In spite of the difficulties in studying bone metabolism in children and the limitations of imaging techniques, the prevalence of decreased bone mineral content seems to be high in HIV infected children.[37,38]

HIV infected children have a lower bone mineral density compared to uninfected children. Patients on HAART have lower lumbar bone mineral density than nontreated HIV infected children and controls. Longitudinal studies indicate that the annual increment in bone mineral density of the whole skeleton is significantly lower in HIV infected children-adolescents than in non-HIV infected healthy controls.[38]

Increased markers of bone formation, such as osteocalcin, bone alkaline phospatase (BALP) and bone reabsorption, such as NTx, deoxypiridinoline or calciuria have been reported in HIV infected children on HAART compared with untreated HIV infected or uninfected children.[37,38] This increase is greater in patients with advanced disease. By contrast, calciotropic hormones (PTH vitamin D) and serum calcium/phosphorus are usually normal suggesting the intake and absorption of vitamin D and oligoelements are not impaired.[34] The evolution of osteopenia in HIV infected children is unknown. Longitudinal studies have shown that there is stability of z-score in the short-term.[37] Nevertheless, the consequences of this decreased bone mineral density is unknown but of great concern due to the fact that the physiological peak value of bone mass density is achieved in young adults and may be permanently impaired in HIV infected children with the subsequent risk of pathological fractures. Although to date, reports of bone fractures are rare, observational data, from the PACTG 219 study indicate that they may be more common in HIV infected children,[39] as has been observed in adults.[34] Supplement of calcium and vitamin D has not demonstrated any benefit, although it is important to assure an adequate intake and exercise in these children. Bisphosfonates have demonstrated some benefit in the treatment of osteopenia and osteoporosis in controlled clinical trials in HIV infected adults[40,41] and should be considered in children with pathological fractures and severe osteoporosis.

Refer to Table 5.8.7 for diagnosis and management of bone disorders.

Table 5.8.7: Diagnosis and management of bone disorders[7]

• Definitions osteoporosis/osteopenia: Following WHO classification: • Reduced BMD (by DEXA) in symptomatic patients • Osteopenia: Z score- BMD< -1 and -2.5 SD (standard deviation) - Osteoporosis: Z score -BMD <-2.5 SD Following the International Society for clinical densitometry: • Low BDM in patients <20 years old : Z score -BMD <-2 SD • Screening for asymptomatic patients is not recommendation • Management - Calcium/vitamin D as a prophylaxis: No benefit has been demostrated, although it is important to assure an adequate intake of both (≥ 500 ml of milk/ day + solar exposition), consider weight control, exercise, avoidance of alcohol, smoking. - Bisphosfonates should be considered in children with pathological fractures and severe osteoporosis plus calcium/ vitamin D. Osteonecrosis • Diagnosis - Physical examination, X-ray, MRI • Treatment - Early: symptomatic, weight control - Surgical treatment if it is required.

Metabolic Considerations before Beginning ARV Therapy

- When an ART is beginning in a child some considerations have to be taken in account: changes in pharmacokinetic parameters with age, availability of palatable drug, complexity of regimen, potential adverse effects, ARV interactions, comorbidities, adherence and possible future regimens. So, although the goal of HAART is controlling morbidity and mortality related to the infection, other issues like drug-related toxicity are important and should be considered when a new ARV regimen is designed.
- For initial treatment, combination therapy must include at least 3 ARVs from at least 2 ARV classes, including a PI or an NNRTI + a dual-NRTI backbone. Salvage therapy is more complex and includes more pills; has more adverse effects and makes more difficult the design of a regimen with a suitable metabolic profile.
- **NNRTI-Based Regimens**: NNRTIs have better metabolic profile (less dyslipidemia, lipodystrophy, etc.) compared to PIs although single point mutations in the reverse transcriptase gene may lead to virological failure and resistance to both drugs. So, it is important to verify adherence of patients before starting them. Nevirapine has better lipid profile than efavirenz but must be used with caution in patients with high-level of CD4 because liver and skin toxicity are more probable and sometimes could be serious.
- **PI-Based Regimens:** These regimens are very efficacious and resistance requires multiple mutations, but are less palatable and metabolic effects (dyslipidemia, lipodystrophy and maybe insulin resistance) are more frequent. Lopinavir/ritonavir and PI boosted with ritonavir are associated with dyslipidemia. Atazanavir seems to have better metabolic profile.

- **Triple-NRTI Regimen:** Less potent than NNRTI or PI-based regimens and is to be considered only in some special cases. Lactic acidosis/hepatic steatosis has been recorded.
- **NRTI profile:** Nowadays, d4T is not recommended because of toxicity and should never be given with didanosine (ddI).[42] Studies performed in adults have shown some evidences of possible cardiovascular toxicity of ABC while on this drug.[42] Although it remains controversial, most adult physicians avoid ABC in patients at high-risk of cardiovascular disease. However, this is less clear in children and as they have low-risk of cardiovascular disease and, ABC is considered as a first-line ART. HLA genotype B*5701 must be performed before using ABC. People with this HLA are at high-risk for ABC hypersensitivity and in these cases therefore, ABC must be avoided. Tenofovir seems to have a better metabolic profile but is not licensed for children <18 years old, and there are concerns about potential renal toxicity and effects on bone mineralization in prepubertal children. The higher rate of bone turnover associated with normal skeletal growth and sometimes, high plasma levels of the drugs could induce higher bone toxicity in children than in adults. Some studies, have observed absolute decline in bone mineral density in children who received TDF. In some cases, BMD returned to baseline after changing but not always. This decrease was more important in younger children. About renal abnormalities, hypophosphatemia seems to be common but reversible following TDF withdrawal. It should not be used together with ddI because adverse effects could happen more frequently. PIs potentiated with ritonavir also increase TDF levels. Therefore when TDF is used careful monitoring is indicated. It can be used in adolescents, who could also benefit from taking Atripla (EFV+tenofovir+FTC), a once-daily formulation, which is recommended first-line in adults.[43,44]

Risk Factors for Cardiovascular Disease (CVD)

There is an evidence that adults with HIV infection are at an increased risk of developing premature atherosclerotic CVD associated with abnormal metabolic profiles that have been previously described. In children this problem might be higher than in adults, as they may live longer with HIV and undergo ARV therapy for a longer time. Some studies have described possible risk factors.

Miller et al, compared HIV infected children and NHANES controls (American National Cohort, HIV negative). They showed HIV infected children have lower weights, heights and BMIs but have similar waist circumferences and subscapular skinfold. Risk factors for CVD were higher triglycerides and lower HDL-cholesterol compared with control group. PIs were associated with worse lipid profile (higher LDL-cholesterol), NRTI with greater visceral fat and NNRTI with more beneficial lipid profile (higher HDL and lower visceral adipose tissue).[45] Aldrovandi et al, reported another study wherein HIV positive and negative infected children were compared to show the distribution of morphological and metabolic outcomes in these two groups and in two groups of vertically HIV infected children on ARV (PI users and non-PI user). They also found that HIV infected children had lower weights, heights and limb fat than HIV negative children. Between children on ARV, a high prevalence of lipid abnormalities and insulin resistance were observed among those on PIs regimens (mainly ritonavir and nelfinavir) compared to non- PI users (mainly nevirapine and efavirenz).[46] Nevertheless, some lipid alterations can improve at the beginning of ARV therapy, so therapy could be also beneficial. Favorable lipid changes have been observed associated with CD4 increases, suggesting a protective effect of immune reconstitutions on atherosclerosis.[16]

Finally, some reports have shown changes in carotid intima-media thickness (a surrogate marker of CVD in the general adult population) in HIV infected subjects.

A recent study, has found higher changes in carotid intima-media thickness in HIV infected patients than in healthy controls at baseline, although, at 48 weeks, these changes were similar between groups. The authors suggest that these data show that HIV infected children/young adults are at high-risk of CVD, but lipid control, immune restoration, and viral suppression with continuous antiretroviral therapy may prevent its worsening.[47] This result supports that HIV-related factors (CD4, viral load) play a role in CVD in HIV infected patients. Adult studies have shown that inflammatory markers and endothelial dysfunction improve with ARV and treatment interruption in SMART has shown increase in CVD-related events.[48,49]

Children with HIV infection compared with controls have adverse cardiac risk factors. PIs and NRTI seem to contribute to this abnormal profile, whereas NNRTI could be beneficial as some studies have shown. The increased CVD risk associated with HIV presents new challenges and serious implications for quality of life and life expectancy for HIV infected patients. Because atherosclerosis formation begins early in childhood, children should be monitored and interventions that improve these factors should be considered as soon as possible. Promoting healthy lifestyles including diet, exercise, smoking cessation, etc should be considered in the management of these patients.

Case Studies

CASE 1

Patient with hypercholesterolemia: A 10-year-old girl who is being treated with d4T + 3TC + lopinavir boosted with ritonavir; previously, she had received ZDV+ddI+nelfinavir. She has undetectable viral load for a long time (3 years) and CD4 25 percent (500 cell/mm^3). She suffered from hypercholesterolemia (total cholesterol 338 mg/dL,160 LDL-cho, HDL –cho 60 mg/dl and TG 112 mg/dl):

1st strategy: diet and exercise 6 months ® Total cholesterol 290 mg/dl, LDL-cho:150 mg,

2nd strategy (simplification)® > Switch from PI to nevirapine [in this case if possible because there aren't resistance mutations to nevirapine, she has undetectable viral load for a long time and good adherence but the change has to be done with caution because she has CD4>250 cell/mm^3, as, adverse events (rash, hepatitis, etc.) with nevirapine are more frequent). She was switched to d4T + 3TC + nevirapine: total cholesterol 240 mg/dl, LDL-cho:130 mg. She remained with viral load < 50 copies/ml. Abacavir could be an alternative if there is no resistance and HLA B5701 is negative.

3rd strategy: Finally, Ezetimibe: Total cholesterol 200 mg/dl, LDL-cho:120 mg. Statins could have been considered instead of ezetimibe but the main problem is drug-drug interactions and toxicity. Nevertheless, if the other measures had failed, statins would have been considered.

CASE 2

Patient with lipodystrophy: An 8-year-old boy who was receiving ZDV + 3TC + indinavir was switched to ZDV + 3TC + nevirapine to make his regimen easier to take, to avoid renal damage associated to indinavir and to improve his abdominal lipohypertrophy. He showed a significant decrease in abdominal fat accumulation at the end of the year. His viral load remained undetectable.

CASE 3

Patient with hypercholesterolemia and lipoatrophy: A 17-year-old boy who was receiving ZDV + 3TC + lopinavir/ritonavir suffered from hypercholesterolemia, facial lipoatrophy and in the last months bad adherence. He asked for an ARV interruption. ARVs were withdrawn considering bad adherence and that he has a stable immunovirological situation. However, close monitoring was done. Hyperlipidemia and lipoatrophy showed a little improvement. ARVs were resumed after one year when adherence was better (TDF, FTC and efavirenz).

APPENDIX-5.8.1

Short-term drug class effects[7,27,42]

- Before beginning a new regimen the patient has to be aware of the drug-related toxicities and possible interactions with other medications.
- If the patient shows severe or life-threatening toxicity all components of the ARV regimen should be stopped and resumed after resolving. Identification of the responsible drug allows substitution of a similar agent, thereby, avoiding the responsible drug
- If the patient has moderate toxicity, ARVs should continue under close monitoring while an assessment is done to identify the causes
- Change from one drug to another drug to which the patient's virus is sensitive using the same drug class (e.g. change to stavudine for zidovudine-related anemia or to nevirapine for efavirenz-related central nervous system symptoms). Sometimes, change drug classes if necessary (e.g. from PI to an NNRTI due to gastrointestinal intolerance).
- If the patient has mild toxicity, can be treated symptomatically and in many cases drug discontinuation is not needed
- Dose reduction could be done only when drug levels have been determined to be excessive.

Antiretrovirals	*Toxicities*	*Actions*
Zidovudine	Anemia, neutropenia, increased transaminases. Macrocytosis almost 100 percent (used to monitor adherence) Some-times, blue to black discoloration of nails	Monitor blood count. For severe anemia or neutropenia (<500 /uml) reduce ZDV dose or change to another NRTI; sometimes, transfusions may be needed if anemia is severe
Lamivudine	Well-tolerated: Headache, abdominal pain, elevated transaminases. Pancreatitis (abdominal pain, nausea, vomiting) may occur in children who have advanced HIV disease	Monitor amylase and lipase if pancreatitis is suspected. Discontinue lamivudine if it is confirmed and when resolves use another NRTI avoiding ddI or d4T
Abacavir	Potentially fatal hypersensitivity reaction in 5 percent (very rare in Africans); usually occurs in first 6 weeks of treatment. ("flu-like" symptoms, fever, rash, malaise, nausea, vomiting, diarrhea, abdominal pain, lymphadenopathy)	Ask for HLA-B*5701 test before starting; if available and if it is positive abacavir must be avoided. Warn patients about hypersensitivity and monitor symptoms. If reaction is progressive or severe, drug should be stopped and don´t give again because deaths have been reported

Contd...

Contd...

Emtricitabine	Well-tolerated: Headache, diarrhea, nausea, rash, all usually mild. Hyperpigmentation of soles and palms.	Warn about possible adverse effects
Tenofovir	Renal toxicity and reduced bone mineral density (BMD) with osteopenia	Monitor renal function, including for proteinuria. Headache, nausea, vomiting, renal tubular dysfunction, bone demineralization, exacerbations of hepatitis on discontinuation. BMD could be monitored with DXA
Didanosine	Nausea, diarrhea (may be formulation dependent). Pancreatitis. Lactic acidosis and hepatic steatosis in combination with ddI, can be fatal	Enteric coated capsules if possible. Monitor jaundice, hepatomegaly, liver function, amylase, lipase, lactate, pH if hepatitis, pancreatitis or lactic acidosis is suspected. Discontinue therapy if confirmed; when resolves, restart antiretrovirals and change to another NRTI (not d4T) and avoid NRTI if lactic acidosis
Stavudine	Pancreatitis, hepatitis, lactic acidosis and hepatic steatosis in combination with ddI, can be fatal. Nausea, vomiting, abdominal pain, sleep disorders	Monitor jaundice, hepatomegaly, liver function, (amylase, lipase, lactate, pH) if hepatitis, pancreatitis or lactic acidosis is suspected. Discontinue therapy if confirmed; when resolves, restart antiretrovirals and change to another NRTI (not d4T) and avoid NRTI if lactic acidosis
Nevirapine	Rash occurs in 16 percent of patients; rash may be severe (8%); Stevens-Johnson syndrome or life-threatening rash have been reported in 0.3 percent. Sometimes, hepatitis that can be fatal. Pharmacy advice on dosing with potentially interacting agents (CYP450 metabolized drugs). Some studies have reported increased nevirapine hepatotoxicity in female patients with CD4 lymphocyte counts greater than 250 cells/ml (especially pregnant women)	Use of 2-week half dose "lead-in" period reduces the incidence of rash. If mild-to-moderate rash occurs during dose escalation, ARV should be discontinued until rash resolves; when ARV are restarted, NVP should be restarted in the initial "lead in" dosing phase. If mild-to-moderate rash occurs after "lead-in" phase, NVP can be cautiously continued while rash observed or EFV can be substituted for NVP. If severe rash, mucosal lesions or systemic symptoms, NVP should be permanently discontinued
Efavirenz	Rash–10 percent of patients, but rarely severe (<1%). Sleep disturbs, nightmare and other central nervous system problems (dizziness, drowsiness). In many cases, resolve in 2-4 weeks. Increased risk of liver toxicity if prior hepatitis B or C. Pharmacy advice on dosing with potentially interacting agents and CYP450 metabolized drugs	Take efavirenz before going to sleep to decrease CNS side effects. Clinical evaluation for rash (no cross-reaction with other NNRTI) Monitor for signs of hepatitis. Discontinue all therapy if confirmed
Lopinavir	Most common: nausea, diarrhea, headache, Hyperlipidemia (cholesterol and TG) Oral solution contains 42 percent alcohol	Take with food to optimize absorption. Symptomatic management of gastrointestinal (GI) symptoms. Monitor lipid profile. Risk of pancreatitis if high hyper TG.
Ritonavir	GI intolerance, nausea, diarrhea, dyspepsia, peri-oral parasthesae. Sometimes hepatitis	Symptomatic management of GI symptoms. Pharmacy advice on dosing with potentially interacting agents and CYP450 metabolized drugs
Nelfinavir	Diarrhea (10-30%) mainly at start of therapy, often resolves on its own in days-weeks	Take with food to optimize absorption. Symptomatic management of GI symptoms.
Indinavir	Renal hypertension, Nephrolithiasis. GI symptoms. Indirect hyperbilirubinemia, Headache, asthenia, blurry vision, dizziness, rash, metallic taste, thrombocytopenia, Lipodystrophy (abdominal fat accumulation) Encourage fluid intake. Monitor for hematuria. Evaluate if flank pain, possibly temporarily discontinue IND, restart after resolves (recurrent nephrolithiasis in 50%). Hyperbilirubinemia clinically insignificant.	Monitor blood pressure. Warn about adequate hydration to avoid lithiasis. Monitor renal function mainly for hematuria. If lithiasis discontinue Indinavir, (recurrent nephrolithiasis in 50% after restarting)
Fosamprenavir	GI intolerance, nausea, diarrhea, headache, rash, peri-oral parasthesae, hyperlipidemia	Symptomatic management of GI symptoms
Atazanavir	GI intolerance, nausea, diarrhea, headache, rash, parasthesae. Indirect–hyperbilirubinemia, normal transaminases, reversible on discontinuation. Less associated with lipid abnormalities, but altered glucose metabolism has been reported	Hyperbilirubinemia could be reversible on discontinuation. Be careful during pregnancy and monitor neonatal hyperbilirubinemia.
Saquinavir	GI intolerance, nausea, diarrhea 10-20% (more common with soft-gel), dyspepsia, hepatitis	Symptomatic management of GI symptoms
Darunavir	Rash, nausea, diarrhea, headache. Contains sulphonamide moiety–check allergies	Symptomatic management of GI symptoms

Contd...

Contd...

Tipranavir	Hepatitis, rash, nausea, diarrhea. Intracranial hemorrhage has been reported.Contains sulphonamide moiety—check allergies	Monitor liver function. Contraindicated in patients with moderate-to-severe hepatic insufficiency
Fusion inhibitor	Injection site reactions, hypersensitivity reactions	Injections site reactions can be managed by education programs
Maraviroc	Nausea, constipation, headache, dizziness, pruritus	Pharmacy advice on dosing with potentially interacting agents
Raltegravir	Nausea, dizziness, insomnia, rash, pancreatitis, hepatitis.	Monitor possible adverse effects

Hepatic Toxicity of ARVs

All ARVs could be associated, although the onset of this adverse event could be different (within 12 weeks of initiation of NNRTI and PI and even months to years of initiation of NRTI).

Toxicity Grading:[51]

Hepatic and gastrointestinal toxicities[51]

	Grade 1	*Grade 2*	*Grade 3*	*Grade 4*
Bilirubin (when accompanied by any increase in other liver function test)	1.1 - <1.25 x ULN	1.25 - <1.5 x ULN	1.5 - 1.75 x ULN	> 1.75 x ULN
Bilirubin (when other liver function are in the normal range)	1.1 - <1.5 x ULN	1.5 - <2.0 x ULN	2.0 - 3.0 x ULN	> 3.0 x ULN
AST (SGOT)	1.1 - <2.0 x ULN	2.0 - <3.0 x ULN	3.0 - 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 - <2.0 x ULN	2.0 - <3.0 x ULN	3.0 - 8.0 x ULN	> 8 x ULN
GGT	1.1 - <2.0 x ULN	2.0 - <3.0 x ULN	3.0 - 8.0 x ULN	> 8 x ULN
Pancreatic Amylase	1.1-1.4 x ULN	1.5-1.9 x ULN	2.0-3.0 x ULN	>3.0 x ULN
Uric Acid	7.5-9.9mg/dL	10-12.4 mg/dL	12.5-15.0 mg/dL	>15.0 mg/dL
Appetite	———————-			
Abdominal Pain	Mild	Decreased appetite	Appetite very decreased, no solid food taken	No solid or liquid taken
Diarrhea	Slight change in consistency and/or frequency of stools	Moderate No Treatment Needed	Moderate-Treatment Needed	Severe-Hospitalized for treatment

- **Clinical manifestations**: Sometimes, only an asymptomatic elevation of AST, ALT is observed. Other clinical manifestations are: nausea, fatigue, jaundice, hepatomegaly or even lactic acidosis and hepatic steatosis (NRTI associated: ZDV, ddI, d4T).
- **Risk factors:** Although hepatic toxicity is uncommon in children, we must be cautioned when some ARVs are used, mainly, nevirapine or tipranavir or when children have other risk factors (hepatitis B or C•, elevated baseline ALT, AST, children who received other hepatotoxic medications, alcohol use, underlying liver disease, etc.) In these patients, obtain AST, ALT at baseline, at 2 and 4 weeks and then every 3 months. If no risk factors, obtain AST, ALT at baseline and at least every 3–4 months and in all cases when hepatic toxicity is suspected.

  For NVP the risk of hepatotoxicity in adults has been observed more frequently in females with pre-nevirapine CD4 >250 cells/mm^3 or males with pre-nevirapine CD4 >400 cells/mm^3. Sometimes, hypersensitivity reaction could be associated with hepatitis due to nevirapine or abacavir.
- **Management:** In asymptomatic patients with ALT or AST >5–10 times above normal limits, consider discontinuing ARVs, although in some specific cases therapy could be continued with close monitoring. Avoid nevirapine and other non ARV drugs that could have risk of hepatotoxicity. In symptomatic patients, discontinue all ARVs and all hepatotoxic drugs and do not restart the offending drug. Avoid NRTIs like ZDV, ddI or d4T if lactic acidosis is suspected.
- Rule out coinfection with hepatitis A,B,C or cytomegalovirus, EBV, etc.
- Indirect hyperbilirubinemia could be observed when atazanavir or indinavir are used, commonly at the beginning of therapy. In many cases, patients are

asymptomatic or have mild jaundice. Monitor bilirubin levels, mainly at the beginning of therapy. Frequently, is not necessary to discontinue the ARVs because hyperbilirubinemia may improve over time.

For more details, please refer to "Gastrointestinal and hepatobiliary manifestations in children with HIV" chapter.

Hematologic Effects of ARVs

Anemia

- Anemia is usually normocytic, normochromic with low reticulocyte counts. The main ARV associated is ZDV. So, children who receive ZDV suffer from anemia more commonly than children who receive other ARVs. The onset of anemia is variable (from weeks to months after initiation). Anemia predicts death independently from CD4 and viral load.

  Causes: Marrow infiltrating infection (CMV, tuberculosis, MAC, histoplasmosis, HIV, parvovirus B_{19} infection, etc.); Tumor (lymphoma); Nutritional (B_{12}, folic acid, iron deficiency); Drug induced marrow suppression (ZDV, ganciclovir, pyrimethamine, phenytoin, etc.); Hemolytic anemia (dapsone, primaquine, etc.).
- **Clinical manifestations**: Commonly, patients are asymptomatic or only show mild fatigue, pallor, tachypnea and in some cases congestive heart failure. In HIV-exposed newborns, ZDV effect may coincide with physiologic hemoglobin decrease.
- **Risk factors**: Low CD4, high viral load, black race, preterm birth, neonatal blood loss, malaria, iron deficiency, hemoglobinopathy and some drugs like trimethoprim-sulfamethoxazole, rifabutin, etc.
- **Management:** Monitor red blood count at birth and at least at 4 weeks for high risk babies and avoid ZDV if anemia is present. Exclude other causes: bleeding (guaiac stools), hemolysis (LDH, haptoglobin, bilirubin), folate or B_{12} deficiency (macrocytic anemia) or iron deficiency (microcytic anemia, serum iron, transferrin, ferritin, etc.). Intervention is recommended if hemoglobin is <7.0 gm/dL or when anemia is associated with symptoms. In these cases ZDV and marrow-toxic drugs could be discontinued and changed to a non-ZDV-containing regimen. In some cases, transfusion could be necessary (symptomatic patients, level of hemoglobin < 7 mg/dl). Erythropoietin 50–200 IU/kg/dose 3 times weekly could be considered with symptomatic and refractory cases.

Neutropenia

- Commonly associated with ZDV, HIV infection or other drugs (ganciclovir, sulfonamides, etc.)
- **Clinical manifestations:** Asymptomatic when neutrophils are >500 cells/mm³ but if <500 cells/mm³ patients could suffer from bacterial infections
- **Risk factors:** ZDV, marrow-toxic drugs (e.g. trimethoprim-sulfamethoxazole, ganciclovir, hydroxyurea, rifabutin)
- **Management**: Monitor white cells at least 3 to 4 times per year. Intervention is necessary if neutropenia is severe (< 500 cell/mm³). Discontinue all marrow-toxic drugs and treat likely causes, (malignancies, infections, etc.). Discontinuing ARVs is not generally necessary but if ZDV is implicated, consider changing to another NRTI if feasible. G-CSF 5–10 mcg/kg once daily, could be considered in severe cases.

Idiopathic Thrombocytopenia Purpura

- Unexplained platelet count <100,000/ml.
- Most cases are due to HIV infection or drugs (heparin, quinidine, TMP-SMX, rifampin, etc.).
- **Management**

Treat HIV infection: effective HAART that leads to viral suppression and CD4 count rebound; Discontinuation of the implicated drug (median time to recovery 7 days). If persistently symptomatic or required for procedure: prednisone, immunoglobulin, Rho (D) immune globulin, splenectomy. If hemorrhage: platelet transfusions plus prednisone.

Hematologic toxicities[51]

	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin for children greater than 12 months and less than 2 years of age	9.0-9.9 gm/dL	7.0-8.9 gm/dL	<7.0 gm/dL	Cardiac Failure secondary to anemia
Hemoglobin for children greater that 2 years of age	10-10.9 gm/dL	7.0-9.9 gm/dL	<7.0 gm/dL	Cardiac failure secondary to anemia
Absolute Neutrophil Count	750-1200/mm³	400-749/mm³	250-399/mm³	<250/mm³
Platelets	----	50,000-75,000/mm³	25,000-49,999/mm³	<25,000/mm³
Prothrombin Time (PT)	1.1-1.2 x ULN	1.3 -1.5 x ULN	1.6 -3.0 x ULN	>3.0 x ULN
Partial Thromboplastin Time (PTT)	1.1-1.6 x ULN	1.7-2.3 x ULN	2.4 -3.0 x ULN	>3.0 x ULN

Skin rash with ARVs

- Many drugs could be associated with skin rash

Frequency	*ARVs*
Common	nevirapine, efavirenz, etravirine, fosamprenavir, atazanavir, emtricitabine
Less common	abacavir, darunavir, tipranavir, tenofovir
Uncommon	lopinavir, raltegravir, maraviroc
Stevens-Johnson Syndrome	nevirapine, efavirenz, etravirine, fosamprenavir, abacavir, darunavir, zidovudine, ddl, indinavir, lopinavir, atazanavir
Systemic hypersensitivity reaction	abacavir, nevirapine, enfuvirtide

Skin rash with Non ARVs

Sulfonamides, NNRTI or PI that contain a sulfonamide moiety (fosamprenavir, amprenavir, darunavir, tipranavir), phenytoin, cephalosporins.

- **Clinical manifestation**

Rashes may appear after the first few days of initiation to weeks after starting therapy. Most rashes are mild-to-moderate, diffuse maculopapular eruptions, urticaria, morbilliform eruptions and a large number of drug interactions, but sometimes, could be a manifestation of systemic hypersensitivity. NNRTIs have resulted in various cutaneous eruptions, as well as a hypersensitivity syndrome. NRTIs have resulted in alterations of the nails, nail and mucocutaneous pigmentation, hair changes, vasculitis, and morbilliform eruptions.

Stevens-Johnson syndrome, erythema multiforme major, toxic epidermal necrolysis: skin eruption plus mucous membrane ulceration, blister/bullae that can progress to skin necrosis, conjunctivitis plus systemic symptoms (fever, tachycardia, malaise, myalgia, arthralgia, etc.).

Systemic hypersensitivity reaction: Abacavir: flu-like symptoms (fever, diffuse rash, headache, abdominal pain, pharyngitis, etc.); can mimic anaphylaxis.

Nevirapine: Flu-like symptoms, rash, hepatic failure with encephalopathy; Dress syndrome (drug rash with eosinophilia and systemic symptoms).

Local injection site reaction with pain, erythema, induration, nodules and cysts, pruritis, ecchymosis, mainly when efuvirtide containing regimens are used. Systemic hypersensitivity reaction has also been described.

- **Risk factors**

Nevirapine: Naïve patients with CD4 count >250 cells/mm^3 in women and >400 cells/mm^3 in men are at greater

Skin and other toxicities[51]

	Grade 1	*Grade 2*	*Grade 3*	*Grade 4*
Allergy	Pruritus without Rash	Pruritic Rash	Mild Urticaria	Severe Urticaria Anaphylaxis, Angioedema
Drug Fever (Rectal temp)	-	38.5-40°C 101.3-104.0°F	Greater than 40.0°C Greater than 104.0°F	Sustained Fever: Equal or greater than 40°C (104°F) for longer than 5 days
Cutaneous	Localized rash	Diffuse maculopapular Rash	Generalized urticaria	Stevens-Johnson Syndrome or Erythema multiforme
Stomatitis	Mild discomfort	Painful, difficulty in swallowing, but able to eat and drink	Painful, unable to swallow solids	Painful, unable to swallow liquids; requires IV fluids
Clinical symptoms not otherwise specified in this table	No therapy; monitor condition	May require minimal intervention and monitoring	Requires medical care and possible hospitalization	Requires active medical intervention, hospitalization, or hospice care
Laboratory values not otherwise specified in this table	Abnormal, but requiring no immediate intervention; follow-up	Sufficiently abnormal to require evaluation as to causality and perhaps mild therapeutic intervention, but not of sufficient severity to warrant immediate changes in study drug	Sufficiently severe to require evaluation and treatment, including at least temporary suspension of study drug	Life-threatening severity; Requires immediate evaluation, treatment, and usually hospitalization; Study drug must be stopped immediately and should not be restarted until the abnormality is clearly felt to be caused by some other mechanism than study drug

risk. More common in adult females. HLA-DRB 101 is associated with high risk of rash with nevirapine or efavirenz; patients with HLA-B*5701have more risk of systemic hypersensitivity reaction with abacavir. Caucasians have more risk than blacks or Asians. Screen for it before beginning abacavir if feasible. If positive, do not use abacavir.

- **Management**[7]

Prevention: Start nevirapine using half of the total dose (once daily for 2 weeks) and then escalation to target dose with twice-daily dosing. Do not use corticosteroids during nevirapine dose escalation. Warn patients about rash and systemic symptoms.

Ask for AST and ALT in patients with rash and at baseline, at 1 and 2 weeks and then every 3 months.

Avoid nevirapine in women, especially if pregnant and if they have CD4 >250 cells/mm^3 or in men with CD4 >400 cells/mm^3 if feasible.

Do not use nevirapine in post exposure prophylaxis.

Grades of rash	*Management*
Mild	Antihistamines Medication can be continued with caution
Moderete	Antihistamines Medication can be continued with caution
Severe	Discontinue all ARVs and drugs that could be implied Do not restart the possible causative medication. Experts recommend to avoid NNRTI if SJS, EM, TEN. Monitor ALT and AST when rash is associated with nevirapine-containing regimen.
Stevens-Johnson syndrome (SJS) **Erythema multiforme major (EM)** **Toxic epidermal necrolysis (TEN)**	Discontinue all ARVs and drugs that could be implied Do not restart the possible causative medication. Intensive care support could be needed. Corticosteroids and/or IVIG have been used in severe cases with different results Experts recommend to avoid NNRTI if SJS,EM, TEN.
Systemic hypersensitivity reaction	Discontinue all ARVs and drugs that could be implied (cotrimoxazole, hepatotoxic medications, etc.). Do not restart the possible causative medication (nevirapine, abacavir, etc.) Check other causes for hepatitis. Intensive care support could be needed.
Local injection site reaction	Rotate injection sites and massage area after injection.

Most common adverse cutaneous reactions associated with the new antiretrovirals[50]

ARV	*Adverse cutaneous reaction*
lopinavir/ritonavir, darunavir	maculopapular rash
fosamprenavir, amprenavir, atazanavir, tipranavir	skin rash
efavirenz, nevirapine	skin rash and DRESS syndrome
etravirine	skin rash
tenofovir	skin rash
abacavir	hypersensitivity reaction
emtricitabine	skin rash and skin discoloration
raltegravir	skin rash and diaphoresis
maraviroc	pruritic rash

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5.9

Adherence to Antiretroviral Therapy in Children—Challenges and Strategies

Cherie-Ann Pereira, Mamatha M Lala, John Farley

Introduction

"There is no hope left, everyone has given up – the doctors, the nurses, the social workers and now... me too. My son left us and so is my grandson following suit...what am I to do...How can I go ahead? Is there anything that can keep him by my side for as long as I live?" (Grandmother, HIV negative, 75 years)

Prior to the advent of Antiretroviral Therapy (ART), this would have been the plea of most grandparents of HIV positive children. The grandmother quoted above believes in miracles—all thanks to ART, her grandson's health has turned around for the better, leaving us with a smiling, healthy naughty boy just like any other. Today, the need to address the HIV epidemic through care, support, treatment and prevention efforts is of utmost importance. The impact of this epidemic has hit every level of society—households, agriculture, industry, education and health sectors. Economic and social development achievements are now wearing away on account of the widespread HIV infection; resulting in reduction or loss of income, fewer crops are planted or harvested as farmers are too ill to work, large number of dropouts from school due to the great financial burden or formation of child-headed families. The healthcare system is on the brink of collapsing with the rising number of People Living With HIV/AIDS (PLHWA) while individuals have to deal with suffering and death.

In the mid 1990s, the introduction of antiretroviral (ARV) medicines in developed countries completely transformed the Human Immunodeficiency Virus (HIV) infection from a fatal illness to a manageable disease, thus improving the lives of PLWHA. At the end of 2007 the World Health Organization (WHO) estimated that there were about three million people receiving antiretroviral therapy (ART) in the low-income and middle-income countries, representing 31 percent of the estimated population who need it. The survival of these people has increased with the introduction of Highly Active Antiretroviral Therapy (HAART). Over the last few years, the provision of ART in the resource constrained settings of developing nations, although challenging, is on the increase. They have managed to overcome barriers such as high medicine prices and lack of political motivation at the national and international levels and thus have been able to make ART widely available to the masses. However, there still exist several limitations such as poor or inadequate healthcare facilities, insufficiently trained personnel, lack of proper administration and persons with ulterior political motives within the healthcare system. Hence, an urgent need has arisen to scale up physical and human resources to cope with the increased need of ART and carry on stringent monitoring of adherence to this treatment regimen. This wonder therapy utilizes a combination of antiretroviral agents—nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), etc. to suppress viral replication and reduce the possibility of developing HIV mutations which could lead to the development of drug-resistant viral strains. ART also allows the CD4 count to increase, thus enhancing the immunologic response to Opportunistic Infections (OIs). It is observed that suboptimal treatment adherence is associated with virologic, immunologic and clinical failure. This chapter aims to emphasize on the need and importance of adherence as a social and biological process and the strategies for the same.

The Need for Adherence (Fig. 5.9.1)

Adherence to ART has been defined as "the ability of the person living with HIV/AIDS to be involved in choosing, starting, managing and maintaining a given therapeutic combination medication regimen to control viral (HIV) replication and improve immune function".[10] It connotes the patient's participation and engagement in maintaining a regimen he or she believes will be beneficial, strongly implying a therapeutic partnership with providers, which

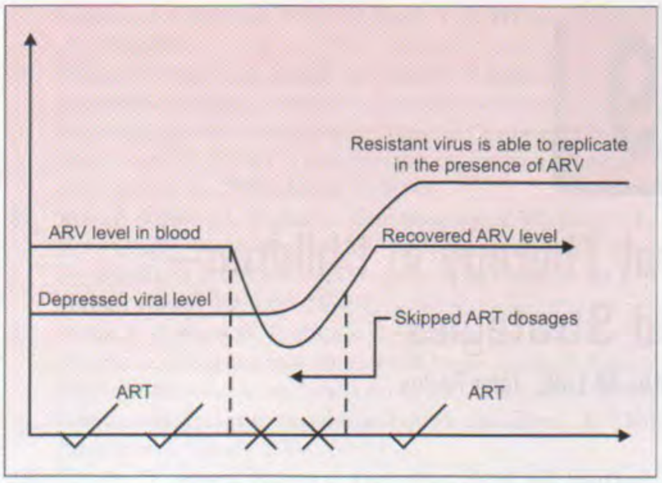


Fig. 5.9.1: The development of drug resistant viruses

Ref: Van Dyke, 2008

is essential for the patient to successfully follow the prescribed treatment. It is the degree to which a patient exactly follows a prescribed treatment regimen in the context of a consultative partnership between the clinician or the healthcare worker or counselor. In order for the HIV treatment to work effectively, drugs must be taken on time, every time, i.e. 100 percent medication adherence. Poor adherence may negatively impact a drug's effectiveness. Improved health outcomes for the HIV infected persons will not be achieved without maximal viral suppression. HAART represents a major breakthrough in HIV management, but not all patients respond optimally to this treatment. Nonadherence is well-established as a major cause of clinical failure, and intermittent non-adherence is a particular problem, seen especially in children and youth. Studies in adults have demonstrated that > 95 percent adherence to HAART is necessary for adequate suppression of viral load.[1-3] In the presence of selective pressure by antiretroviral agents, high rates of viral replication and viral mutation lead to the development of drug resistance. The World Health Organization (WHO) defines HIV drug resistance as the ability of HIV to mutate and reproduce itself in the presence of antiretroviral drugs. Mutations conferring resistance against one antiretroviral agent often confer cross-resistance to other agents; poor adherence can thus render a whole class of antiretrovirals ineffective.

The most crucial time after the initiation of ART is the first six months. Clinical and immunological improvements are not very apparent and drug toxicities may emerge. Some patients fail to respond to the treatment or may even exhibit clinical deterioration initially. Complications arising in the first few weeks after ART initiation are very common in patients with severe immunodeficiency, i.e. when the immune system's ability to fight disease is compromised or almost absent. The failure of a patient with an advanced HIV infection to show an immediate response does not necessarily indicate a poor response to ART. It takes a while by the time the immune system is strengthened and ART is able to control viral replication. As a patient gradually recovers immune function, exacerbation of previously subclinical infections like tuberculosis may occur, resulting in the worsening of the disease. This does not indicate failure of therapy, instead is the result of immune reconstitution. Such symptoms might be interpreted as a poor response to ART; however it is important to allow sufficient time for the therapy to take action before judging its effectiveness and considering the possibility of development of immune reconstitution inflammatory syndrome (IRIS) in the first few months of ART. At these times, the switching of ART would not be advisable.[4]

Most antiretroviral (ARV) drugs used by adults are available in pediatric formulations as well. While experienced pediatricians should establish guidelines and provide training of healthcare providers caring for HIV infected children, it is critical that ART care for children be widely available at all levels of the health system. ART in children is adjusted to suit the age and weight of the child. It has the following functions:

- Preserves or restores immune function (CD4 cell count)
- Provides sustained suppression of the viral load
- Promotes or restores normal growth and development
- Improves the quality of life
- Prevents complicating infections and cancers
- Prolongs the child's life and improves the quality of life.

ART in children must be considered when there is an early diagnosis of HIV infection or when a baby or child is diagnosed late because an HIV related symptomatic disease develops. Good adherence to drug therapy is crucial to achieve a good viral and immunological outcome.[5,6]

The following factors may have an impact on adherence in children (Table 5.9.1):[6]

- Affordability of ART—Before initiating ART the healthcare professional should make sure the parents/caregivers of the child can afford a proposed treatment regimen over a prolonged period of time. The counselor must be able to prepare the parents/ caregivers for this large step.
- Motivation and commitment of the parents/ caregivers to the child's lifelong therapy—Caregivers need to understand that adherence involves giving every dose of medication, one to three times daily, every day of every year.
- Parents/caregivers need to anticipate and plan for picnics, schooling and other activities in advance, to avoid missing any dose.

- The healthcare professional and counselor play an important role to make the parents/caregivers understand that poor adherence is the most important factor in drug failure and resistance. Good adherence needs to be emphasized, along with strict monitoring systems.

"Drugs would not work if people would not take them". Nonadherence is a global problem seen in all illnesses. According to WHO, adherence to long-term therapies averages at 50 percent in developed countries and is assumed to be even lower in the developing ones.[7,8] Persons with chronic illnesses must adhere to a medical regimen even if there is no cure, in the absence of visible symptoms. Currently, our knowledge of HIV therapy is only gradually progressing, thus life long treatment is required. Pediatric nonadherence is also a clear concern for the entire healthcare system.

Table 5.9.1: Factors associated with adherence

Patient and family factors	*Associated with better adherence*	*Associated with poorer adherence*	*Inconsistent association*
Demographics Patient/caregiver characteristics Socioeconomic status		• Patient of adolescent age • Lower socioeconomic status • Caregiver's lower educational level • Language barrier • Single parenthood • Rural location	• Gender • Race • Culture • Traditional practices • Societal pressure
Psychosocial Parental/ caregiver Traits Family traits Parental supervision	• Supportive • Flexible • Warm and loving • Problem solver • Not overly critical • Active • Good listener	• Caregiver depression • Hostile • Stressed • Poor coping skills • Low health motivation • Discord • Inadequate • Restrictive	• Judgmental attitude • Religious and moralistic perspective
Peer group	• Peer support • Peer counseling	• Fear of being ostracized from the group	
Factual knowledge	• Better parental knowledge	• Lack of knowledge	• Patient knowledge
Adjustment to disease/coping skills	• Good coping skills	• Maladaptive (anger, denial, anxiety) • Mental illness • Cognitive impairment • Development delay	
Disease factors		• Long duration • Asymptomatic disease • Severe symptoms causing functional impairment • Presence of side-effects	
Regimen factors	• Simplified • Nonaversive • Nonintrusive • Nocturnal dosing • Curative	• Prolonged • Complex • Aversive • Intrusive • Unpalatable • Noncurative	
Provider factors	• Familiar • Empathetic • Good communicator • Friendly	• Impersonal • Apathetic • Poor communication skills	• Lack of proper storage facilities • Lack of hygiene and cleanliness
Health system factors	• Convenient location • Good accessibility • Supportive staff	• Distant location • Poor accessibility • Long waiting times • Unfriendly staff • Untrained staff	• Corruption

Ref: Adapted from 'Patient Treatment Adherence – Concepts, Interventions and Measurement' – Hayden B, Bosworth, Eugene Z. Oddone, Moris Weinberger

There are two kinds of nonadherence namely:

1. **Unintentional nonadherence:** Most commonly seen in pediatric care, which results from human error. Some common examples include, forgetting medicines prescribed, misunderstanding instructions, missing appointments and running out of medication. Poor knowledge and communication also contribute to this type of nonadherence.
2. **Intentional nonadherence:** This is less common as it is more difficult to detect. Some examples include discontinuing medications due to occurrence of side effects, perceived ineffectiveness of the medication and concerns about safety or resistance on the part of the child. Cultural, ethnic and religious beliefs especially in developing countries which base their lives greatly on traditional practices and customs also have a significant impact on intentional nonadherence.

ART adherence in adults is related to the following factors (Table 5.9.2):

- Characteristics of the individual and his or her environment
- Treatment regimen
- Family and Caregivers' support
- Healthcare provider and client—provider relationship
- Healthcare setting.

Combinations of any or all of these factors contribute to enabling an adult to strictly observe his/her treatment regimen. Whereas adherence problems in children are multifaceted, the prime issue is that young children are dependent on caregivers for their medications. The physical, economic and psychosocial issues surrounding HIV/AIDS that affect the family/caretakers will affect the child's care and how the child's ART is managed. Ideally, the expertise of an entire multidisciplinary team is critical in dealing with medical, nursing, social, psychological and nutritional aspects of adherence support.

There are a few key issues that make ART in children different from that in adults, they include:

- Diagnosis of HIV infection in infants
- Pharmacokinetics (how they are absorbed, distributed, metabolized and eliminated in children)
- Viral load levels
- Psychological issues
- Socioeconomic issues
- Developmental issues.

Giving lifelong drugs to a child is not only difficult but also stressful for the family. Although the availability of first line fixed dose combination formulations for children have improved this challenge, many of the older and second line antiretrovirals are unpalatable and after a few doses the child either refuses the medication or vomits it. Therefore, it becomes extremely essential to prepare the child and the family well prior to the initiation of ART. Healthcare providers and counselors need to educate parents/caregivers about the developmental needs of the children, especially discipline and medications. Younger children need ritual, consistency and supervision; taking medications the same time, at the same place and same way each day is comforting for children in the younger age group.

Table 5.9.2: Social and pharmacological aspects before starting ART

Social aspects	*Pharmacological aspects*
• Motivation to begin therapy • Ability for the patient to adhere to the long-term therapy • Lifestyle pattern of the patient • Economic stability of the family • Existence of family support • Knowledge of the pros and cons of starting the therapy	• Dosing and frequency of the drugs • Tolerability of the regimen • Access and availability of drugs

An adolescent's approach to illness is very different from that of adults. Those who get infected in their teenage years face challenges while adhering to their medication regimes, for reasons such as:

- Denial, anger and fear of their HIV infection
- Associated myths and misconceptions
- Distrust in the healthcare system
- Lack of belief in the effectiveness of medications
- Low self-esteem
- Stigma, discrimination and fear of being shunned away by society.

The radical thought processes of adolescents make it difficult for them to take lifelong medications, especially when they are in the asymptomatic stage. In addition, they have to bear the side effects of the medications. Denial, irritation and depression are also commonly seen amongst this age group, the daily medicines sometimes serve to be a reminder that they are suffering from this disease. Adolescents struggle for independence from their parents, authority figures and societal pressures. An adolescent who was previously compliant as a child could rebel against parents/caregivers with regards to medications or care. Hence, there arises a great need to have an efficient monitoring system to support and motivate children through their developmental stages enabling them to understand the importance, cope and deal with the need to adhere to their ART regimes.

The success of ART is affected by several factors in the resource constrained settings of the developing world, which include (Fig. 5.9.2):[8]

- Lack of motivation to begin therapy
- Lack of ability to adhere to therapy

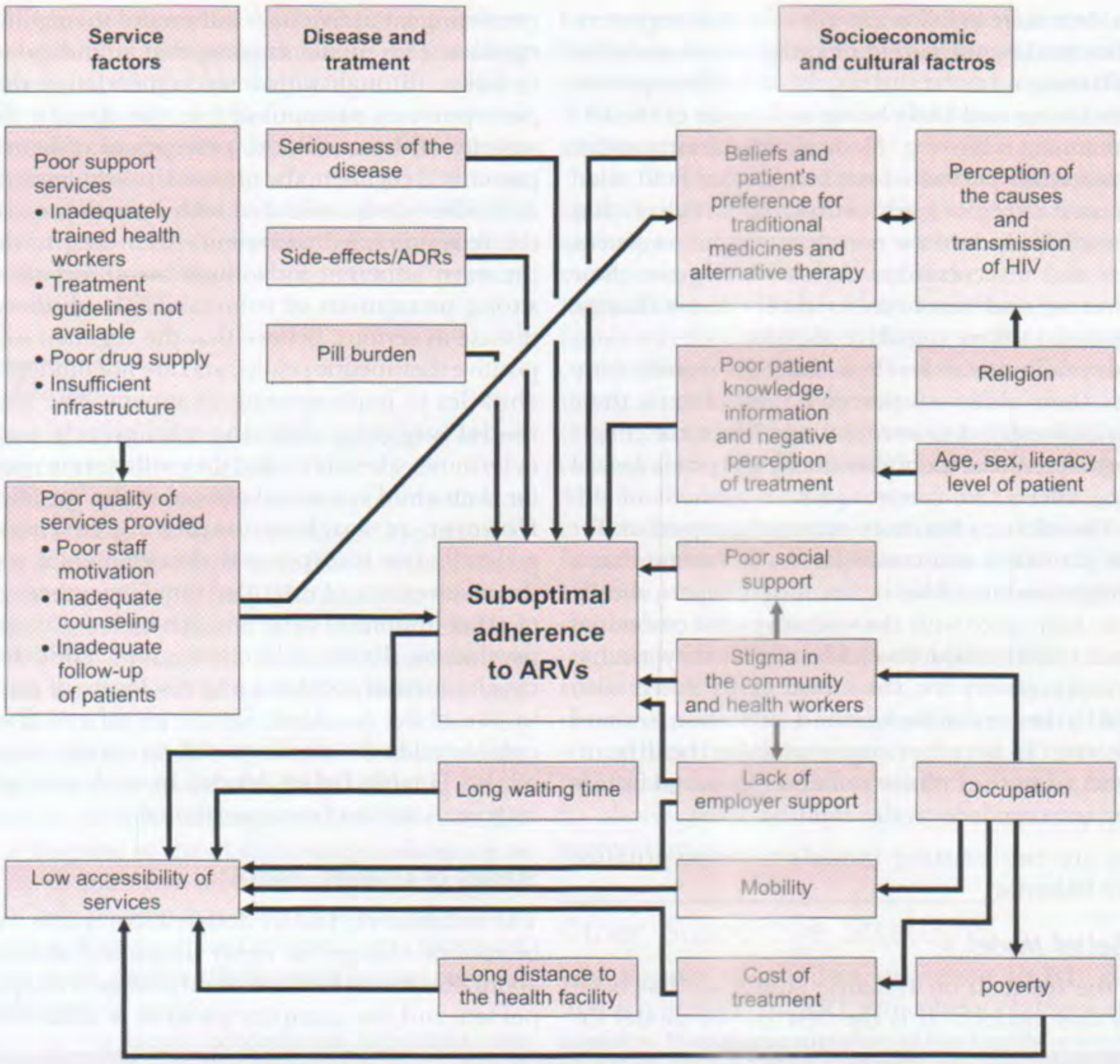


Fig. 5.9.2: Factors contributing to suboptimal adherence to ARVs

Ref: Access to Adherence: The Challenges of Antiretroviral Treatment – Studies from Botswana, Tanzania and Uganda, WHO, 2006

- Advantages and disadvantages of initiating therapy
- Life-long duration of ART
- Lifestyle pattern
- Lack of access to proper nutritious food
- Lack of financial support and family support
- Tolerability of the regimen, dealing with side effects
- Emergence of resistance
- No proper access to primary medical care
- Availability of drugs
- Dosing frequency
- Lack of accurate knowledge provided to patient
- Illiteracy and stigma against HIV/AIDS in society
- ART not being curative.

ART Adherence not only varies between different individuals but also in the same individual over time. Hence, it becomes extremely essential for supportive interventions at various levels namely, patient level, medication level, healthcare level and community level to boost adherence and the overall impact of ART (Table 5.9.3).

One of the greatest challenges today is Pediatric ART adherence. In this case caregivers are responsible for the adherence of children and so have a profound impact on adherence. Children living in families in which the adult caregiver is ill, are subjected to significant stress, lack effective organizational skills, lack social support, or are not motivated to administer medications and will have a high risk of nonadherence. On such occasions the need for outreach staff to provide additional support for families with such challenges may enhance adherence.

Often children have to follow complex medical regimens, this is influenced by the parent or caregiver's knowledge of the illness, understanding of the therapeutic recommendations and lastly being well aware of the fact that the treatment is lifelong. Medical practitioners, social workers and other personnel working in this field need to emphasize caregiver education, and realize that adherence will likely decrease over time without consistent follow-ups and interventions. As children grow, their understanding and reactions to their illness change corresponding to their cognitive abilities.[9]

The developmental level of children significantly influences their ability to perceive their illness, their treatment and respond to interventions. Thus, the child's level of cognitive, motor, social, emotional, and psychological functioning affects the course and management of the disease. Therefore, it becomes extremely important for healthcare providers and counselors to be certain that a child's understanding of his or her illness is periodically updated to keep pace with the cognitive and emotional development of the child. As children grow they assume greater responsibility for their own care, this is also influenced by their social background, education, sex and peer pressure. It becomes imperative for healthcare providers to assess the influence of developmental factors and adjust interventions as the child matures.

There are two existing models to conceptualize adherence behavior:

Health Belief Model

Much of the research on Pediatric adherence has been driven by this model.[23] It is the best known model for predicting an individual's adherence to ongoing medical regimes. This model suggests that an individual's ability to follow through with a recommendation depends on perception of susceptibility to the specific illness, the severity of the condition, perceptions of benefits of the prescribed regimen, the physical, psychological, financial and other costs associated with initiating or continuing the recommended treatment. According to this model, the most adherent individuals are those who maintain strong perceptions of vulnerability to disease, view the disease as serious, believe that the regimen will produce positive therapeutic results, and are not hindered by many obstacles to implementing treatment. The health belief model suggests that the caregiver's perspective determines whether or not they will assume responsibility for their child's care and adhere to the specific regimen. However, researchers employing this model have generally not incorporated developmental concerns or the involvement of extended family members. A number of other important determinants such as caregiver stress, psychiatric illness, addiction issues, child behavioral/ developmental problems and disclosure of the diagnosis to the child or other family members also are not considered in the classic model. As a result, the relevance of the Health Belief Model in pediatric adherence interventions has been questioned.

Stages of Change Model

The initiation of HAART and its adherence is a significant behavioral change for newly diagnosed adolescents and youth. Readiness for behavioral change is unique for each person and the complex process is addressed by this

Table 5.9.3: Strategies supporting adherence

Regimen-focussed	*Child-family-focussed*	*Provider-focussed*
• A simplified regimen like twice-a-day dosing is the best option. Regimens with a low pill burden or volume (for liquids) can be chosen • All medications taken by the family must be reviewed periodically; to discontinue those that are unnecessary. • The healthcare worker can help families identify ways to mask bad tasting powdered or liquid medications, especially for infants • Younger children need to be taught how to swallow tablets. Crushing the pills can help in this process, however it is important to identify medications that should not be crushed as they are enteric coated • A fixed dose combination tablet, available in different strengths which is formulated to dissolve in water will be used in the future. This is however still under study	• Older children must be involved in their adherence assessments, positive reinforcements and words of encouragement could be used • Even if children are given responsibility for their medication, supervision by the family is essential • Formation of support groups encourages families to share what works for them and their children • Regular assessments must be conducted to ensure the family's capability to be able to deal with a problem that they could face • A progress chart marking out the increasing CD4 counts of the child or decreasing viral load will physically show the effects of medication	• A patient-provider relationship needs to be one of trust, respect and collaboration achieved through communication and active listening • It is important for the provider to be available and accessible to the family especially when the regimen becomes more complex • It is important for the provider to be aware of the patient's cultural background and beliefs. Thus, the provider is able to understand the patient's perspectives and will advocate for suitable protocols • The provider needs to be aware of the medical culture as well, to share his/ her own perspectives, make recommendations and offer alternatives to the family

model.[24] This model describes a pattern of movement through five specific stages: individuals are (a) unwilling or unaware to do anything about the problem, (b) consider the possibility of change, (c) become determined and prepared to make change, (d) take action and (e) sustain the change over time. It is important to note that an individual may not progress linearly through the different stages; therefore the healthcare providers must carefully assess an individual's readiness for action (i.e. adherence) before prescribing ART.

Pre-ART Phase

There are several aspects that must be kept in mind before the initiation of ART these include (Table 5.9.2):

Most problems with adherence occur within the first or second week; therefore it becomes extremely important to plan for a good start. Assessing the readiness of the child is a crucial step before initiating ART. The family members or siblings need to be involved in and agree with the treatment regime of the child. In countries like India especially, it is very important for the head of the family/identifiable and reliable caretaker to be part of the discussion. It is also very important to obtain an explicit agreement on the need for treatment and for adherence. Alongside, assessing family beliefs, traditions, lifestyle, environment and priorities, the ability and willingness of the child to take medications as well as success or problems observed with earlier medical regimens can help plan strategies for successful adherence. Nonadherence is likely to occur if adherence to a treatment had failed previously, thus specific interventions are required to address the existing problems.

Education of the family becomes an important step before the initiation of ART. Imparting of correct knowledge about the disease through creative strategies, the purpose of ART and the importance of adherence needs to be stressed on. An entire system of extended family members, friends and healthcare workers, who can support adherence needs to be identified. Home visits to teach about medications can be carried out to allow families to learn about medications in an environment they are comfortable in, besides this the home environment is also assessed for its feasibility to allow adherence. Families also need to be prepared to deal with any crisis that may arise in the process; a plan of action in such situations can be drawn out together with them. A simple schedule that works with the family and their lifestyle must be drawn out so as not to disrupt their routine functioning. Most often, families are uneducated or have very poor reading skills; therefore syringes for oral liquid medications can be marked, special needs and bottles can be given a color-code to match the schedule, pictures can also be used to ease the process. A trial run with 'dummy pills' following the real schedule can be conducted for a week to let the family get a feel of the future therapy. Above all, constant follow-ups especially at the beginning are extremely important to monitor the treatment and support the family. A follow-up plan must be devised focusing on both, short and long term adherence.

In developing countries due to the existence of agriculture, daily wage earning, construction labor or working in shifts, a family may not have regularly scheduled meal times or a lifestyle that fits the schedule for taking medications consistently. Any deviation, due to loss of a family member, migration, change or loss of employment could throw a medication schedule way off its course. At times, a parent or family member may have a different drug regimen and schedule from that of the child's, thereby causing confusion or an additional burden on the family. The family needs to be prepared for the developmental and behavioral issues of children. Children show improvement if medication becomes a part of their daily routine, provided parents are consistent and supervise the child while taking medication.

Lastly, families need to be prepared for the common side-effects such as nausea, vomiting, skin rash or diarrhea. Sometimes, families stop treatment out of fear when faced with unexpected side-effects without informing the physician or nurse. It must be made clear to always seek medical advice before stopping any medication.

Other Supportive Strategies

Maintenance of confidentiality about an HIV diagnosis makes adherence to ART difficult for children and their families. If only one member of the family is aware about the diagnosis, medications cannot be stored or taken openly. It is important that healthcare providers and counselors together with the families recognize that disclosure is a process. Supporting the family during the disclosure to the child is extremely important as the child is unable to understand why he/she has to take medicines. Disclosure to the other family members or friends may provide a supportive person to give medications to the child and provide encouragement to the family. However, most often due to societal pressures, stigma and discrimination and the misconceptions existing in society, disclosing the status of the child could lead to the child being ostracized from the community he/she has been living in. For the same reason, many families are reluctant to disclose the status of the child to the school authorities, playgroups, local clubs, etc. for fear that the child may be ill-treated or asked to leave.

Once an entire support system has been put into place, the healthcare provider, family and child can initiate ART as prescribed by the physician. WHO recommends that accurate assessment of adherence is necessary for an

effective and efficient treatment plan.[7] Decisions to change recommendations or medications to promote adherence depend on valid and reliable measurements of adherence. Without such an assessment, providers will be unable to identify adherent and nonadherent patients, thus timely and vital interventions will be overlooked. Therefore, adherence needs to be measured in clinical settings. Accurate and reliable measures of adherence along with knowledge about the barriers and facilitators of adherence will help researchers identify clinical outcomes and make recommendations for patients who require assistance with their treatment regimes. Measuring adherence to ART is even more challenging as there is a possibility that different classes of ARVs may require different adherence levels to sustain virological suppression; the HIV virus too, responds differently to different levels of adherence. Hence, adherence measurement is fundamental and improved tools need to be developed to assess the trend.

Measurement of Adherence

Adherence measurement provides an opportunity to encourage the adherent patient and to flag patients that require support to improve their adherence. Without an assessment of adherence the opportunities for further interventions are lost. Therefore, the measurement of adherence, including the history of dosing, is the first step towards the design and implementation of interventions to improve adherence. These interventions in turn not only help enhance quality of life but also increase longevity. Today, the measurement of ART adherence of patients has become a major challenge because of the subjective and private nature of pill-taking behavior in patients. Adherence is also affected by the existing healthcare system, the socioeconomic condition, stage of the disease, internal and external support systems and other drug-related factors. Research suggests that adherence to medication in children with HIV infection is a complex process influenced by multiple factors, including demographic, health, medication characteristics and psychosocial characteristics of the child and family. Therefore, if medication adherence is the goal, efficient monitoring and psychosocial support to the family is absolutely essential. At the same time, quantitative assessment of adherence using reliable tools is a challenge with disease management. Till date several methods have been used or proposed to assess adherence in practice or research studies. Each method has distinctive benefits and drawbacks. Optimal adherence is the compliance to ART that achieves a sustained plasma drug concentration that will inhibit viral replication. It is clear that close to 100 percent adherence is necessary for sustained viral suppression; however the cut-off for an adequate level of adherence varies depending on the assessment method used. The adherence cut-off value may also vary with different antiretroviral therapies.

Currently Available Measurement Tools

The methods for adherence assessment can be grouped into two categories:

Direct and objective measures

1. Directly observed treatment (DOT)
2. Therapeutic drug monitoring (TDM)
3. Biomarkers
4. Medication event monitoring system (MEMS)
5. Pill count (PC)

Indirect measures

1. Lifewindows
2. Caregiver interview or self-report (including Computer Assisted Self Interviewing—CASI)
3. Pharmacy records
4. Visual analog scale (VAS)
5. Pill identification test (PIT)
6. Provider Assessment
7. Appointment Keeping

Directly Observed Treatment (DOT)

The DOT method has health workers directly administer medicines to patients. This method confirms adherence as the healthcare worker observes the patient taking the medicine.[11] Thus, it is an objective way of measuring adherence. It can be highly effective in private settings with uninterrupted care. However, DOT does require high costs, can stigmatize the patient, violate confidentiality, be paternalistic and may require complex logistics for the lifelong treatment of HIV/AIDS.

Therapeutic Drug Monitoring (TDM)

In the TDM method, measurement of drug levels in the blood is observed. It is not routinely used to measure adherence. Also, in some ARVs, like nucleoside reverse transcriptase inhibitors (NRTI), blood levels may not directly deduce the levels inside HIV infected cells and so other laboratory markers are used. Therapeutic drug monitoring for patients in still being researched in adults and has been proposed for children with the goal of maintaining levels sufficient enough to suppress viral load and prevent viral mutation and resistance. As pediatric drug monitoring protocols are developed, it will be important to assess the utility of trough drug levels as an adherence assessment tool. The evaluation will require incorporation of other adherence measures for comparison within protocols utilizing therapeutic drug monitoring. This method will only reflect adherence behavior during a period of time, prior to obtaining the

level, depending on the drug metabolism; it does not facilitate assessment of adherence over a continuum. The expenses related to conducting therapeutic drug measurements on a long term basis are not very feasible for use in developing countries.

Biomarkers

Biomarkers can be used to monitor adherence by adding secondary nontoxic medicines to indicate that primary medication was taken. For example riboflavin can be added to the medication and its level can be checked in the urine—the availability of riboflavin in the urine concludes that the drug was administered. There are also indirect biomarkers that can be used. For example, macrocytosis would develop with zidovudine administration. Thus, if macrocytosis is noted, one knows that the drug has been administered. However, the proportion of the prescribed dosing will not be known.

Medication Event Monitoring System (MEMS™)

Electronic methods offer a more detailed assessment, demonstrating problems with dosing intervals in addition to missed doses. The Medication Event Monitoring System (MEMS™) is now the state-of-the art method of evaluating adherence. It contains an electronic device (microprocessor) fitted to the caps of pill containers which records the removal of the cap along with the date and time, it has been found to be reliable in recording dosing histories of ambulatory patients. Several groups in the developed countries are using this method in ongoing studies of HIV infected children. However, electronic tools also pose similar challenges as the previously mentioned ones. These caps are not designed for bottles containing liquids or powders, so this approach has generally not been used for children receiving medications in those formulations. Caregivers or youth who lay out pills in advance or use a pill box storage device are also excluded. Usage of this technique requires caregiver cooperation and/or pharmacist collaboration; caps may become defective or lost, resulting in incomplete data. Other problems with MEMS include patients opening the bottle but not taking the pill, patients decanting pills and measuring only one medication at a time. Today SmartCap™ has been developed which provides patients with a reminder beep when doses are due and an information 'window' telling them when last the bottle was opened. This is attractive as a combined monitor and intervention for older children.

Pill Count (PC)

The pill count method to estimate adherence involves a comparison between the amount of medication remaining in the child's bottle and the amount that should be remaining; based on the amount and dosage of the initial prescription and the length of time since the patient began using the bottle. Pill dumping, as mentioned earlier is the greatest challenge faced during the use of this method; at times the parent may not leave all unused pills in the bottle in an effort to falsely increase the apparent level of adherence to please the clinician. In studies with adults, unannounced pill counts conducted in the home were reported to be more robustly associated with biological outcomes.[28] Also determining the date when the patient started using the current bottle is another challenge. The pill count method can be utilized with liquid formulations by utilizing a liquid measurement device. Pill counts, although labor intensive are likely to be the most practical and readily available non self-report adherence assessment tool. A recent study in HIV infected children and adolescents demonstrated a more robust association between viral load and adherence measured by pill count compared with caregiver or child self-report, but incomplete data for a large proportion of study participants highlighted the logistical challenges.[25]

Lifewindows (Fig. 5.9.3)

Lifewindows is a personalized, interactive and engaging stand-alone software program designed to help HIV infected patients and caregivers to achieve and maintain adequate ART adherence. "Marcus", the onscreen video host, welcomes users, guides them and provides personalized feedback. The program adapts to the needs of the user and tracks each user's adherence and barriers to adherence over time. This is a highly informative, involving and interactive experience. Users select their medications; give details of their regimen and the number of doses they are supposed to take. ART adherence is assessed over a 3-day and 3 to 4 week period. Based on the self-reported barriers to ART adherence, users are provided with a list of adherence-promoting strategies and select a strategy to work on during their LifeWindows



Fig. 5.9.3: Lifewindows

session. The program contains 20 different theory based interventions that address a variety of unique adherence related barriers. By assessing a PLWHA's specific ART adherence related deficits and by providing users with tailored computer based interventions, it is anticipated that LifeWindows will be effective at increasing and maintaining ART adherence in an efficient and costeffective manner. This method is still very recent and under research study in the developed world, the extent to which it would assist adherence in the developing world where almost half the population is unable to read or write is questionable.[12-14]

Computer Assisted Self-Interviewing (CASI)

Computer Assisted Self Interviewing (CASI) cannot be used for routine data collection on adherence as it depends on information technology which is not universally available. Patients collecting their medications regularly on a due date are assumed to be adhering to treatment. There is also, the audio computer assisted self interviewing (ACASI) that encourages more honest answers from patients on sensitive topics rather than face-to-face interviews. This method could possibly replace the traditional face-to-face interviewing regarding adherence, particularly for older children and adolescents. Adherence related questions which indicate the understanding of the patient on how to take the prescribed medication is one of the other models that have evolved.

Pharmacy Records

Maintenance of pharmacy records is one of the indirect methods for measuring adherence. The chances of pill dumping or reporting bias are minimized in this case. This involves the comparison of refill data from the pharmacy with estimated refill requirement if all doses were administered. This method is less labor intensive than the pill counts, but it does require pharmacist collaboration or access to healthcare data. A special feature of pharmacy records as a proxy for measuring adherence involves that the method can generate a refill list and indicates patients not reporting for refills. Drawbacks of using pharmacy records include that they serve only as proxy of ingestion of medicine; it requires the patient to use the same pharmacy each time along with electronic tracking. In general, the method overestimates adherence, since the availability of medication at home does not necessarily mean that it was actually administered. However, if utilized over several months will help identify adherence problems. Enhanced adherence to therapy will be possible if this method is combined with pill counts to improve sensitivity.

Caregiver Interview or Self-report

The caregiver interview or self-report could be prone to bias, as at times parents may inflate their adherence report to satisfy clinicians. On the other hand, it can be used to identify poor adherers, who can respond to interventions. Parent self-monitoring involves using a calendar to record doses given, this is subject to the same bias as caregiver interviews or other approaches to self-report when used as a measurement tool. The caregiver self-report to assess adherence among HIV infected children has been utilized with useful but inconsistent results. The best known instrument is the IMPAACT Network Pediatric Adherence Questionnaire Modules 1 and 2.[26] Module 1 of the Questionnaire begins with identification of antiretroviral medications and then asks the subject about doses missed during the prior 3 days. Module 2 presents a number of potential problems with adherence and asks the caregiver if any of these potential problems have occurred in the past two weeks. Good adherence as assessed by self-report instruments is associated with good clinical outcomes. A study using the PACTG instrument in HIV infected children enrolled in a clinical trial involving a HAART regimen found a correlation between the child's virologic outcome and caregiver self-reported adherence during the three days prior to the interview.[15] Even though self-report instruments can predict clinical outcomes, the data obtained in this manner may not be entirely accurate. It may be possible to improve self-report questionnaires to enhance their accuracy. It is observed that participants are more likely to self-report adherence difficulties when questions focus on problems rather than missed doses. A recent small study of HIV infected children and youth found that self-report strategies other than the 3-day recall such as reporting if any doses were missed during the prior month were more robustly associated with viral load.[27] There is a need for culturally appropriate adherence self-report instruments to be validated in the setting in which they will be utilized.

Visual Analog Scale (VAS)

VAS is a measurement instrument that tries to measure a characteristic or attitude that is believed to range across a continuum of values and cannot easily be measured directly.[16] In order to measure adherence the patient is asked to place a mark somewhere along the line from 0 to 10 that best describes their adherence, this method has the potential for use in resource constrained settings. However, measurement errors also occur with the use of this method. Thus ART adherence measurement with VAS alone is not completely reliable or valid.

Pills Identification Test (PIT)

The Pills Identification Test (PIT) uses a display board with two similar pills called 'twin pills' for each antiretroviral prescribed and asks the patient to identify which pill they are taking. Correct PIT scores have been associated with adherence in HIV infected adults. The features of PIT

include reliability, particularly at the initial phase of treatment, correlation with validated self-report adherence measures and as a remote marker of the actual pill intake.[11] The limitation with this method is that there is loss of sensitivity in measurement for patients who have been on treatment for a long period of time.

Physician Assessment

The estimate of the physician or the clinical judgment of adherence has been studied in adults with chronic illness. Studies indicate that clinicians also take a chance when judging whether or not a patient is adherent. In a study of HIV infected adults, physician adherence assessment was found to correlate poorly with pill counts.[17] Pediatricians too, appear to be just as inaccurate as physicians caring for adults while estimating patient adherence. A small study demonstrated an unexpectedly high reliability for provider assessment in HIV infected children. This study showed that physicians relied heavily on pharmacy refill records and virologic responses,[18] thus suggesting a useful strategy for clinical practice.

Appointment Keeping

Caregivers and patients are provided with regular appointments to maintain continuity of their stock of drugs and thus adherence. If patients are required to be present for follow-up visits to refill prescriptions, being late for a follow-up visit or missing visits immediately indicates an adherence problem, and this information is readily available to clinic staff. Even if patients do not miss any appointment, the adherence rate must be assessed by other methods.

The Need for a Multimethod Approach

As we have seen, some of the adherence measurement tools have been validated to be precise and sensitive in measuring adherence, however the majority of the tools currently used cannot meet all the features of an ideal tool. Thus, it is evident that there is no 'gold' standard in the measurement of adherence. This has led to the need for a multimethod approach combining feasible self-reporting and reasonable objective measures in the measurement of adherence. This tool can include self-report and different combinations of other methods such as PC, PIT, VAS and other electronic methods.

In resource limited settings, the simple self-report questionnaires, pill counting and VAS have been found to be the most effective[19] as compared to adherence using the Medication Event Monitoring System (MEMS caps), record of pharmacy refills, provider assessment, caregiver self-report and appointment keeping. It was found that the best correlation to optimal viral suppression was with the combination of MEMS caps, (although expensive and problematic) and the pharmacy refill records. Provider assessment and appointment keeping was also associated with virologic response. The caregiver self report was not found to be reliable in this case. Above all, there is increasing evidence that adherence interventions should employ a multidisciplinary approach involving healthcare providers, doctors, social support networks, family and friends. Combinations of interventions that complement each other to improve adherence must be considered. This captures not only the effectiveness of the combined multi-intervention but also the specific effectiveness of the different components of the multiple adherence interventions.

Challenges

The formulation and implementation of an adherence measurement poses a number of challenges such as:

- Availability of evidence about the utility of the adherence measurement
- Identifying a measure that meets desired but realistic features and benefits
- Adapting the measure to the peculiarities of the environment where it will be used.

The evidence of the utility of adherence measures can be summarized in the following statement by WHO, "measurement of adherence provides useful information that outcome-monitoring alone cannot provide, but it remains only as an estimate of a patient's actual behavior...without formal assessment, providers are unlikely to accurately identify adherent and nonadherent patients, missing the opportunity for reinforcement and constructive interventions respectively".[7]

Providers are also equally responsible for patient adherence behavior which can be attributed to their paternalistic perspective and misconceptions that patients are to be blamed for nonadherence.

In the developing world, there is a need for the adherence measurement tool with the following features and benefits:

- Objectivity in measuring adherence
- Internal consistency
- Positive predictive value
- Appropriate for use in resource-constrained settings (simple, nonelectronic, user-friendly and quick to administer).

The development of such a tool or use of a multimethod approach that would best serve the purpose is still under extensive research. At the same time, it must be ensured that healthcare providers, HIV clinicians and providers who use the tools available are given updates and lessons on using the tool and implementation of associated interventions.

Other deterrents that hamper the outcome of ART are its lifelong duration, side-effects, complex newer regimes arising due to the development of resistance and the fact that the therapy is not curable. Adherence keeps varying from one individual to the next and low or suboptimal adherence is exhibited at some point or the other during the course of the treatment.

Suboptimal adherence puts forth the following implications:

- Failure of the treatment regimen
- Increase in morbidity and mortality
- Concomitant viral or bacterial infections
- Emergence of resistant strains of the virus: Intermediate levels of adherence are likely to lead to the development of virus with resistant mutations in the genome.[20]

Assessment of Adherence

Family

Assessing how families are managing medications should be part of every clinic and home visit. It is an important part of treatment and will help build trust and good provider-client communication. It is more important to focus on family strengths and work with families in addressing treatment related behaviors and family environmental conditions, rather than blaming the caregivers (and nonadherence) for rises in viral load. When discussing antiretroviral therapy and the importance of adherence, it is important for the clinician to ask the family how they would like the assessment of adherence to be carried out so that their child can get the best benefit form the medications.

It is vital for the healthcare provider to keep in mind the following during the initial months of therapy:

- Assumptions that the family understands the child's medication or regimen must not be made
- The family members must be aware of the name, dose, time and reason for each medication
- The caregiver must be able to demonstrate correctly the dosage of liquid medications to the provider before initiation of therapy
- A system to monitor prescription refills must be developed
- If any dose/s has been missed, the caregiver must feel comfortable sharing this information with the provider
- Regular updates and contact needs to be maintained with families to see to it that they are efficiently managing their medications
- Posters of medications in the office or clinic can be displayed to aid assessment.

Visits to the homes of patients are very helpful in assessing patient adherence. If planned around medication time, a great deal can be learned about how the family is coping with the regimen. As families are more relaxed in their own environments, they are better able to learn, discuss problems and identify possible solutions. Perfect adherence is very difficult for anyone. Thus, the purpose of assessment is to identify problems, provide support and help the family resolve any problem.

Adolescents

Adolescents will tend to say what they would like the clinician to hear or expect from them. Therefore, it is important to let them know that one is genuinely concerned about them. In this case, it is crucial not to blame anyone but to adopt a problem-solving approach. Adolescents who have been infected perinatally and are long term survivors have always had a parent or another family member present during their medical visits. As children grow older it is important to allow them some privacy and time away from their parent or caregiver. Encouraging families to provide youth with their own privacy and space is important and a great challenge in developing countries like India or Bangladesh where parents make all the choices for the child right until marriage and sometimes even after. Discussions with adolescents about their goals and how treatment and adherence fit into these goals is an important intervention for youth.

In India, for instance there is complete lack of awareness among the masses regarding ART. Healthcare providers need vigorous training in delivering all aspects of ART. Medical practitioners and healthcare personnel find it difficult to spare enough time for the extended counseling that is needed for the success of any therapy, especially ART. Moreover, an adequate supply of medicines for ART as well as for treating opportunistic infections is essential to achieve the expected adherence to the treatment regimen.

Interventions to Improve Adherence

There is a great need for the adoption of a holistic approach to improve adherence. There are various levels at which one can work right from the individual level to that of the community. Possible interventions that can be carried out are as follows:

At the Patient Level

- The healthcare provider or clinician or counselor needs to establish a good and healthy rapport not only with the child but also with the parent/caregiver and the family
- The age and maturity of the child needs to be kept in mind and information about HIV/AIDS and its course can be imparted with the help of creative media

- The patient's readiness to take the medication and the support of the family must be assessed and established prior to initiation of treatment
- It is important to first discuss the goals of therapy, need for adherence and the outcome with the child and the family
- The child and family need to understand that the initial regimen has the best chance for long term success
- A treatment plan which is easily understood by the patient can be drawn out together with the patient and implemented
- It is necessary to discuss the impact of resistance with the parent/caregiver and what needs to be done if doses are missed, delayed or vomited
- Daily or weekly pillboxes, timers, alarms or even electronic toys can be used to remind children about their doses
- For patients and families with low literacy levels, visual aids and audio/visual information sources can be used to impart correct information and get rid of misconceptions
- Behavioral skills such as goal-setting, assertiveness/communication and problem solving and behavioral determinants like daily routine, eating, sleeping, schooling, college, recreational activities, etc. are necessary to ensure adequate adherence.

At the Medication/Treatment Level

- There is need to implement a tailor-made regimen for each patient after thoughtful consideration of the simplicity or complexity of the regimen. Pediatric fixed dose formulation tablets which can be dissolved in liquid for administration are less complex and may present fewer palatability challenges than syrups
- Medications prescribed must be readily available at and the nearest possible hospital or clinic
- The school or college timing of the patient along with the job timings of the parent/caregiver must be kept in mind while setting the time for the doses
- It is important for the healthcare provider to convey the common side-effects of ART to the patient and family before starting the therapy. Side-effects that arise can be treated as soon as possible
- The dietary pattern needs to be monitored and the consumption of healthy and nutritious food must be ensured
- Adverse drug interactions should be avoided between ART drugs and those used for other symptoms and opportunistic infections
- It is essential to detect any intervening illness and opportunistic infection as soon as possible.

At the Healthcare Delivery Level

- It is extremely important to establish a healthcare team comprising of well-qualified clinicians, psychologists, nurses, social workers and volunteers to cater to the varying needs of HIV patients
- The attitude of medical staff must be supportive and nonjudgemental
- The doctor must become an educator, friend and information source for the child, who should view this relationship positively
- Each facility should be well-equipped with clean and hygienic storage facilities for the drugs, computers and other such technology to accelerate and enhance the accuracy while working
- Regular trainings and workshops must be conducted with healthcare personnel in order to update them about the latest advances in the field and better ways of dealing with the patients
- Barriers to appointment keeping such as long travel time to pediatric ART points of service, long waiting times, and excessive fees should be addressed
- Providing services to address basic and other health needs such as water purification, nutritional supplements, and insecticide treated nets facilitate comprehensive care and motivate appointment keeping
- Caregiver education and support groups can be offered during waiting time at health facilities.

At the Community Level (Fig. 5.9.4)

- Awareness programs could be carried out, use of television, print media, radio and the internet to sensitize the general public about HIV/AIDS is extremely important
- Various activities for behavioral and attitudinal change can be conducted to help remove stigma and discrimination against PLWHA
- Organizations working on issues related to HIV/AIDS and with PLWHA can encourage adherence through educational sessions and practical strategies
- Adolescents can form support groups to help them cope up with the situation while some others can become peer educators
- Links can be established with vocational training institutions and employment agencies for the proper rehabilitation of these persons
- Research studies on the need for rights of PLWHA, gathering of statistics and cases studies can be done to put forward recommendations to the Governing bodies for policy change

The TASO Model of Community Support–An example for the future.

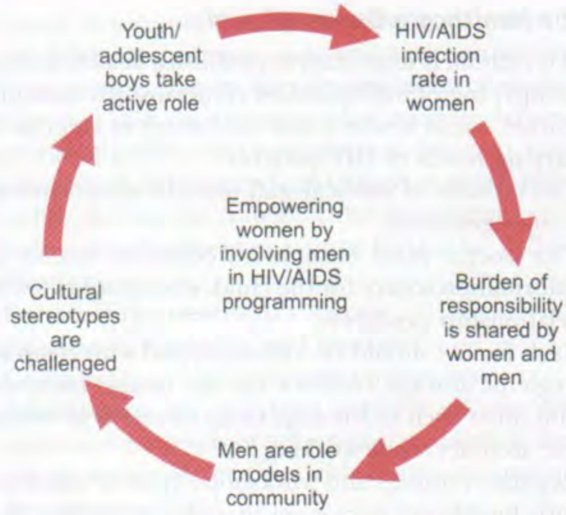


Fig. 5.9.4: An example of interventions at the community level

Ref: Report on Global HIV/AIDS Epidemic, UNAIDS, July 2002

The AIDS Support Organization (TASO) was founded in 1987 in Kampala, Uganda out of the great need to respond to a growing crisis. The TASO Community initiative is an excellent example which calls for community involvement in HIV/AIDS care. The training center equips individuals to respond to and provide specialized care for persons living with HIV/AIDS, thus dealing with the dynamics of the illness in Uganda and beyond. TASO exists to offer counseling, medical care, social support, advocacy and consultancy. A study was carried out in the TASO Mulago clinic in Kampala. Patients were identified and registered at TASO if found to be HIV positive. These patients were then assessed as to whether they were required to initiate HAART. Before enrollment, the patient was asked to identify a medicine companion like a spouse, friend or relative who will help with adherence. After enrollment, the patient was given medicines for three days and assessed for adherence. If he/she took the pills for three days, he/she was given medicines for two weeks. If adherence was still good, he/she was given drugs for two months and thereafter for 6 months. Patients found to have poor adherence were given appointments for adherence counseling. As per this model, routine clinic visits continue after enrollment when HAART drugs are dispensed and adherence assessed; at two weeks, two months and then at six months. The follow-ups depend on the patient's performance in terms of improvement and adherence exhibited. These follow-ups are conducted by TASO's trained field staff from the community itself. This study showed that the majority of patients attending the TASO clinic exhibited good adherence as compared to those who did not. This can be attributed to the continuity of care and close support of the patients which is the hallmark of TASO. Therefore, replication of such models in other regions of Africa and outside becomes extremely necessary.[29]

Role of Education, Information and Counseling Interventions (Table 5.9.4)

An underlying component to improve ART adherence involves increasing client, caregiver or provider knowledge. Cognitive interventions help improve the knowledge of a participant in the intervention. This is especially important in HIV treatment where a clear understanding of the different forms of infection and the role of treatment for a better quality of life exists. Experts have argued that understanding the relationship between adherence and viral load and disease progression affects adherence behavior. Sometimes, knowledge does not always translate into belief; it is only a step towards achieving the goal. Detailed knowledge about the working of ART may not necessarily promote adherence. Instead the belief that ART prolongs life and can possibly postpone death may be sufficient to promote high adherence. In developed countries it was found that a higher level of adherence was associated to those who believed in the effectiveness of ART.[22] Thus, knowledge of and belief in ART may be promoted through educational interventions, which can be in the form of group sessions involving only patients or caregivers, providers, members of the community or any combination of these. These discussions could be held in a unidirectional manner or a participatory approach could be used. Educational interventions can be used before the initiation of treatment or ongoing during treatment at regular intervals. Evidence indicates that ongoing educational interventions may have the highest long-term impact.

Table 5.9.4: The educational continuum

Left side	*Right side*
Direct, educational instruction	Patient-initiated problem solving
Power concentrated in healthcare worker's hands	Patient's independent self-care actions
Survival skills can be taught	Counselor can be used only as a consultant
Spirit of paternalistic concern	Spirit of support
Direct instruction/information provision	Initiative for ongoing problem-solving
The patient may choose not to problem-solve (inspite of counselor's best attempts)	Patient has to make complex self-care decisions

Interventions to improve knowledge are usually combined with other behavioral support interventions. Counseling is a form of educational and social support; it is also a potential mechanism for improving adherence. Counseling and education serve to be the foundation of several interventions and must be delivered in combination by healthcare professionals. Some ART adherence educational counseling interventions are based on already existing theories. One such theory is the 'selfefficacy theory', built on the belief that a person is capable of organizing and executing a particular course of action that is required for a particular activity. This personalized approach tries to boost client morale, skill development and self-sufficiency leading to a noteworthy effect on adherence. In this strategy a technique called 'motivational interviewing' (MI) is used. It is basically a client centered, goal-directed counseling style that was originally developed to treat substance abuse and later adapted for varied behavior-change interventions.[22] This client centered technique allows patients to participate actively and identify problems and barriers to treatment adherence.

ART Adherence Counseling

Antiretroviral therapy should be deferred until patients are prepared to commit themselves to life-long treatment and to maintain good adherence to the therapy. Adherence counseling thus becomes an important aspect during the course of medication. It is the counselor or the healthcare provider who determines whether the patient is ready to initiate ART or prepares the patient for its initiation. This type of counseling involves the counselor along with the healthcare team who work together with the clients and develop personalized plans to ensure adherence. The counselor focuses on enabling the patient, parent/caregiver to understand the importance of adhering to medication, the consequences of poor adherence as well as providing medications which minimize changes to the patient's lifestyle. ART adherence counseling involves education of the patient and parent/caregiver at three different stages which include before ART initiation, ART initiation and treatment-related strategies. In the course of the consequent counseling sessions, predications are made as to whether the adherence is good or poor. Based on these predications the counselor moves ahead with the patient.

Most patients need both direct instruction as well as their participation in problem-solving along with the counselors. In order to strike an effective balance, ART counselors must develop skills to move back and forth along the continuum, keeping their patient's needs and concerns in mind. The central area of the continuum is therefore characterized by active exchange of ideas, clearly negotiated goals and objectives and shared power and influence that serve patients' interests and help foster patient self-management and long term behavior change.

Impact of Financial Incentives

The provision of financial incentives to patients or their families for taking medications poses a number of ethical concerns as to whether the patients is taking the drugs because of the potential reward or because they believe that they are improving their health. This strategy was basically started to enroll and maintain patients in HIV/AIDS services. However, there is no evidence about financial incentives serving to be a mechanism to improve adherence to ART. In addition to this, the feasibility of this strategy in the developing countries is also questionable.

Impact of Technology Interventions

In the high-income settings of the developed world, participants were given instruments or devices which served as reminders to trigger the patient to take the required dose of medication at a particular time. Some researchers argue that communications devices like pagers, alarms, text messaging and telephones can have a greater impact on improvement of adherence rather than education, counseling or other supervision strategies. These communication devices identified have had a positive impact on client adherence. However, as mentioned earlier, the high costs, lack of proper infrastructure, high levels of illiteracy, large populations and societal stigma in the global south will serve as obstacles during use of such devices. The human and infrastructural constraints differentiating resource-constrained settings from high-income settings need to be taken into consideration while developing adherence interventions. The implementation of assessment measures will simply require additional commitment and effort to understand the local and individual circumstances and environments to ensure that the goals of optimal adherence, reduction in viral load and better health are achieved.

The Way Ahead—A Biosocial Approach

A biosocial approach to adherence relies on the dynamic analysis of the clinical and social course of the disease and the continuous interaction of biological and social processes over time.[21] Pathology embedded in social experience captures a series of factors acting together – such as not taking treatment for the undesirable side-effects, due to lack of money to travel to a health center

or purposely missing doses when one is asymptomatic to pretend that AIDS is not a concern. These factors shape the lives of patients; they internalize the factors and use them to provide meaning to their experience with the disease. For example, exposure to AIDS in Haiti, in the 1980s, generated cultural models of its etiology and expected course, often locally interpreted in terms of jealousy or a curse. Similarly, the social experience of AIDS in rural Haiti is also deeply affected by the advent of effective therapy. The introduction of quality HIV care can lead to a rapid reduction in stigma against the illness. Thus, within the changing context in which disease may take place, adherence level is also likely to change and social and biological circumstances and interpretations of them unfurl.

In the study of life histories of the patients and the interactions of social experience with illness episodes, associations between the clinical and social course of the disease, including stigma, health-seeking behavior or adherence can be generated. Most research studies on adherence to ART share the basic understanding that patients are adherent when they agree to the advice of the healthcare provider and take their medications in a timely manner. However, an overemphasis on pill counting as a plain sum of discrete events tends to limit our understanding of adherence as a more complex process. An approach to adherence that combines not only biological but also social knowledge has been put forward - a biosocial approach. This approach relies on qualitative and quantitative methods, this has a greater possibility of enhancing our understanding of adherence and eventually, improving adherence to ART.

Biomedical research rarely examines the social, economic, political and cultural context in which patients live. There is also lack of information available on the impact of poverty on ART which is particular for patients living in poorer settings. Several direct and indirect economic burdens are borne by patients in these countries which affects their ability to access a steady supply of ARVs and take them on time. These include the cost of missing work, the cost of child care during medical visits, the cost of transportation to a healthcare center, the costs of tests to be conducted in case required and other such costs. Though these costs may seem miniscule for the healthcare professionals and decision makers, bearing these costs often results in difficult household decisions and sacrifices like whether one meal should be skipped or whether the girl needs to attend school or whether the child should work. Besides this, taking the prescribed medications in a timely manner requires the family to provide the child with proper food to fit the drug schedule. Regardless of the problems faced while overcoming these difficulties, the inability of a child and his/her family living in poverty to take medications after initiation of ART is then labeled as 'nonadherence'. In this case the addressal of social and economic causes of failure or lack of proper systems or inadequately qualified personnel to address these causes of nonadherence in the public health set-up are completely ignored. Therefore, optimal adherence can be achieved if multiple causes that shape a patient's adherence are analyzed and studied within the social context; this includes the financing of healthcare systems along with upgrading and cost recovery mechanisms.

A biosocial framework which is grounded in the experience of people infected with HIV can be used to better understand adherence, how it changes over time, especially in deprived settings and the reasons for nonadherence which are not within the control of the patient. Addressing adherence will require the provision of social support to patients, encouraging the interactions between healthcare workers and patients and their families, health centers need to focus on patients rather than the illness, having better drug procurement strategies and using modern technology. In other words there is an urgent need for looking at the issue holistically. This would involve improving and investing in primary and rural healthcare, upgrading of public hospitals and referral networks, recruitment and sustenance of healthcare personnel in the public set-up. Thus, the enhancement of adherence can be achieved if the social, economic and political factors impeding adherence are identified, analyzed and acted upon right now.

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SECTION VI

Miscellaneous Issues

6.1

HIV-1 Drug Resistance

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Introduction

With increasing availability and usage of Anti Retroviral Drugs to combat the ill effects of HIV, the world is facing a new challenge of understanding and overcoming the implications of these unforgiving lifelong regimens, thereby bringing the issue of Drug Resistance to the forefront.

In vivo, antiretroviral resistance is a function of viral susceptibility and the drug levels achieved in the target cells, where viral replication occurs. Higher drug levels can suppress partially resistant viruses. Viral susceptibility of competitive inhibitors (i.e. most antiretroviral drugs except CCR5 antagonists) is expressed as the drug concentration that is able to inhibit virus growth *in vitro* to 50 percent (50% inhibitory concentration, IC_{50}) or 90 percent (IC_{90}), relative to a wild-type reference virus.[1] CCR5 antagonist are allosteric inhibitors, and therefore a reduced susceptibility is indicated by a reduction in the percent maximal inhibition (PMI) ("plateau" effect) relative to the wild-type (WT) control.[1]

Pathogenesis

A critical factor for understanding HIV resistance is that HIV has a quasispecies distribution.[2] Soon after infection with a relatively homogeneous viral population, viral replication ensues at an extraordinary rate: 10^{9-12} new virions are generated every day. Because HIV's reverse transcriptase (RT) lacks proof reading ability, 10^{-3} to 10^{-4} mutations (one or two per genome) are spontaneously generated per replication cycle.[3,4] Given HIV's high replication rate, any single mutant and some dual mutants could be generated per day.[4] Most mutations are deleterious and drive mutant viruses to extinction. Others, have neutral or beneficial effects on HIV's replicative capacity and remain incorporated in the quasispecies.[2]

Variants in the virus quasispecies may have different fitness in different environments.[5] The variant with better ability to replicate in the absence of therapy, the WT variant, predominates before therapy initiation. Mutants with a fitness advantage in the presence of therapy remain at very low levels in the absence of treatment. However, they can outcompete the WT within days after therapy initiation if viral replication is not rapidly averted. Secondary mutations often accumulate in the presence of continued viremia; they compensate the potential fitness losses derived from primary resistance mutations and increase cross-class resistance.

In addition to enabling rapid evolution of HIV resistance, HIV's huge antigenic variation capacity confers other important general advantages to the virus:

a. *Extension of the time of infection within the host.* Antigen variation allows immune escape and continuation of vigorous infection. Extended infection time benefits the virus by increasing the chances for transmission to new hosts.
b. *Re-infection of hosts with immune memory from previous infections.* Antigenic variants that differ from a host's previous infections escape that host's memory response. The distribution of the memory profiles between hosts determines the success of each antigenic variant.
c. *Variation in surface antigens may allow pathogens to attach with variable success to cellular receptors of different host genotypes.* Particular antigenic variants attack some host genotypes better than others.
d. *Variable surface antigens permit enhanced pathogen fitness by allowing colonization of different host tissues.* Some HIV variants have preferential tropism for tissues with lower replication kinetics or reduced drug penetration. Similarly, R5 to X4 tropism switches frequently occur in subjects with advanced HIV infection, allowing infection of T lymphocytes, which is associated with accelerated clinical progression.
e. *Some variants exert antigenic interference with the immune response to others.* For example, a host may first encounter a particular antigenic type and then become infected by or develop a cross-reacting variant through antigenic mutation. The second variant may stimulate a host memory response to the first variant rather

than a new, specific response to the second variant, in a phenomenon known as *original antigenic sin*. In other cases, two coexisting variants may interact with the immune system so that one or both variants benefit from the protection created by the presence of the other through *altered peptide ligand antagonism* or other mechanisms.

The likelihood of developing antiretroviral resistance depends on the relative potency of the antiretroviral regimen and the degree of ongoing replication in the presence of therapy.[2, 4, 6-10] (Fig. 6.1.1) A regimen with small antiviral potency creates a minimal selective pressure to the virus and commonly leads to slow resistance evolution, even if replication persists, unless low genetic barrier drugs are included in the regimen. A more potent regimen that is unable to suppress viral replication leads to an increased selective pressure over the virus, which rapidly accumulates resistance. Finally, a highly potent regimen that suppresses viral replication to minimal levels (below the limits of detection of current assays, i.e. <50 copies/ml of HIV-1 plasma RNA) is typically associated with extremely slow or no resistance accumulation.

In addition, each antiretroviral therapeutic class has a unique adherence-resistance relationship (Fig. 6.1.2) as conceptualized by Bangsberg et al.[11] NNRTI-treated individuals rarely develop resistance at high levels of adherence due to the virological effectiveness of these regimens. Due to their long plasma half-lives, these drugs are very forgiving if the patient misses isolated doses. However, NNRTI resistance develops rapidly when prolonged interruptions of treatment that allow

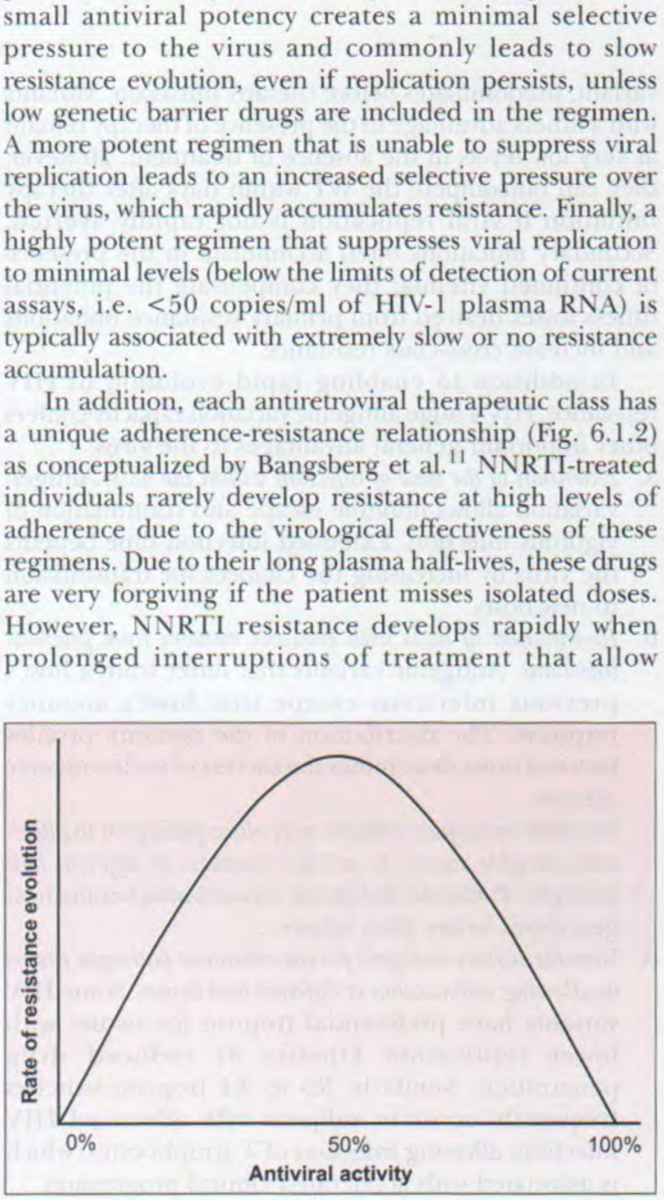


Fig. 6.1.1: Relation between antiviral drug activity and emergence of resistance

Adapted from: Pillay D, Zambon M. Education and debate: antiviral drug resistance. BMJ 1998; 317: 660-62

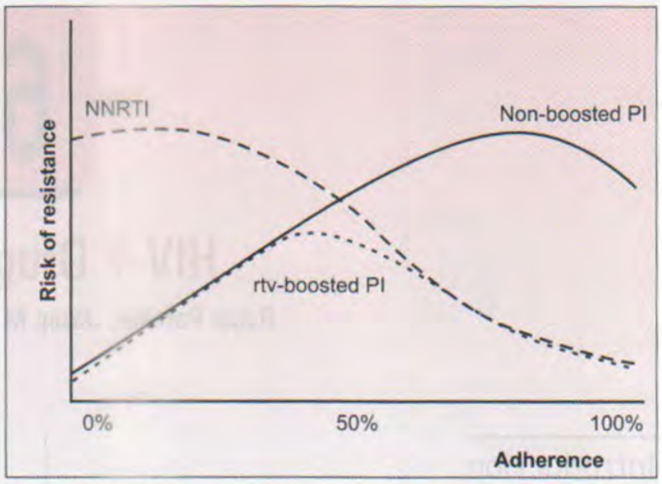


Fig. 6.1.2: Relationship between medication adherence and the risk of developing PI or NNRTI drug resistance.

Resistance to single PI therapy occurs most frequently at moderate to high levels of adherence, resistance to NNRTI therapy occurs at low to moderate levels of adherence, and resistance to ritonavir-boosted PI therapy is most likely to occur at middle ranges of adherence. Data in this figure are conceptual and based on trends observed in a number of recent studies. PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor.

Source: Bangsberg DR, Moss AR, and Deeks SG. Paradoxes of adherence and drug resistance to HIV antiretroviral therapy. J Antimicrob Chemother 53: 696-99

functional monotherapy of the NNRTI during days with plasma levels approaching the HIV-1 IC_{50} plasma concentrations. Furthermore, these mutations confer a low 'fitness' cost. Single unboosted PI-treated individuals may develop resistance at high levels of adherence because residual viral replication is often seen in such patients. PI resistance is uncommon at low levels of adherence because of the significant fitness costs associated with these mutations, and their extremely short terminal plasma half-lives (particularly when boosted with ritonavir). Resistance to a ritonavir-boosted PI is only possible in a narrow range of adherence where there is sufficient drug around to select for mutations that reduce fitness while still allowing residual viral replication.

Attempts to block viral replication through intensified antiretroviral regimens including more than three active antiretrovirals have not demonstrated higher antiviral efficacy than standard 3-drug regimens.[12,13] Residual viral production persists in plasma, body compartments with limited antiretroviral penetration (CNS, testes, kidney, etc) and cellular reservoirs of low turnover or latently HIV infected cells that can reinitiate viral production when needed.[14-20]

Given the molecular structure similarities within compounds of the same antiretroviral family and their

interaction with similar target sites, the emergence of resistance to one drug will often extend to the other drugs of the same class with variable degrees. On the other hand, some mutations conferring high-level resistance to one agent may increase viral susceptibility to another compound, resulting in a so-called "hypersusceptible" virus to the other agent. In addition, many resistance-conferring mutations decrease replication capacity in comparison with the WT virus. The clinical correlates of replication capacity (RC) measurements, are still poorly understood, but are probably clinically relevant. There appears to be a correlation between reduced HIV replication fitness and either clinical outcome or surrogates of clinical outcome (CD4+ T cell counts and viral load), although not all studies found correlations of fitness with both viral load and CD4+ T cell count.[21] Statistically significant associations have been demonstrated between clinical outcomes and a replication capacity assay (Monogram, CA, USA). Higher RC at baseline is also significantly associated with higher HIV-1 RNA, higher CD4 cell activation, lower CD4 cell count, and lower CD4 memory cell count.[22]

Clinical Implications of Antiretroviral Resistance

The most obvious clinical consequence of antiretroviral resistance is loss of treatment efficacy. In general, resistance-associated treatment failure will lead to prescription of more complex, more expensive, less tolerable regimens. Consecutive treatment lines are associated with progressively reduced duration of antiviral efficacy. Each failure is associated with further resistance accumulation; some patients will eventually develop viruses resistant to most drug classes, with very limited options of suppressive salvage regimens.

Moreover, the emergence of antiretroviral resistance among patients starting first-line HAART is associated with a nearly 2-fold increased risk for death.[23,24] Nevertheless, most of the failures in naive patients are related with poor adherence to treatment, and actually these studies are correlating poor adherence with poorer survival. Interestingly, emergence of resistance to NNRTIs seems to be associated with a greater risk of subsequent death (3-fold increase) than emergence of resistance to any other class of drug.

To delay the evolution of antiretroviral drug resistance, it is essential to suppress viral replication profoundly and durably, and manage viral replication rebounds aggressively. The threshold of 20 to 50 copies/ml of HIV-1 RNA has been strongly correlated with durability in clinical studies. Thus, it is established as a universal endpoint in treatment-naive and experienced trials as a robust surrogate of what is called clinically "complete virological suppression"

Mechanisms of Antiretroviral Drug Resistance

Most resistance mutations are simple amino acid substitutions in the proteins targeted by antiretroviral drugs but some include insertions of one or more amino acids. In general, resistance mutations alter the 3-dimensional structure and biochemical properties of viral proteins or co-receptors, reducing the activity of drugs through a variety of mechanisms.

Nucleoside and Nucleotide Analog

Resistance to nucleoside and nucleotide analog can be summarized in four different pathways: the M184V/I mutation; the thymidine-analogue (TAM) 1 and 2 pathways; the K65R and L74V pathway, and the multinucleoside resistance pathway, which includes the Q151M and/or 69 insertion complexes.

Mutations M184V, K65R and the Q151M complex promote resistance by selectively impairing the ability of reverse transcriptase to incorporate an analog into DNA. Conversely, TAMs induce removal of the nucleoside analog from the 3' end of the terminated DNA chain. This process involves an ATP- or pyrophosphate-mediated attack to the phosphodiester bond linking the nucleoside analog to the DNA chain.[25,26] Entry of ATP and pyrophosphate, a by-product of DNA polymerization, is facilitated by the structure of a reverse transcriptase expressing TAMs.[3] However, such entry is significantly decreased in the presence of the M184V mutation, which explains the difficulty for TAMs to emerge in the presence of M184V.

The M184V/I Mutation

Mutations M184V (ATG→GTG) and M184I (ATG→ATA) in the conserved YMDD motif of the HIV-1 reverse transcriptase (RT) induce high-level lamivudine and emtricitabine resistance[27-31] by altering the interaction between the enzyme's active site, the primer/template duplex and the incoming deoxynucleoside triphosphates.[32] Lamivudine resistance develops very early when this drug is given in monotherapy[29,33] or in combination with zidovudine or stavudine.[8,34,35] The M184I mutation is the first to emerge, being detectable as early as 7 days after the initiation of treatment,[29] because of the mutational bias in the RT toward G→A replacements.[36] Under the continuous presence of the drug, viruses harboring the M184V mutation emerge because they are more fit than wildtype and M184I mutants.[37] M184V variants can be detected as early as

3 weeks after starting lamivudine therapy and become fixed in virtually all subjects after 12 weeks.[29] Likewise, M184V is the first and most likely resistance-related mutation to arise in subjects with active replication under any lamivudine-including 3-drug ART[38-40] and in those undergoing structured treatment interruptions (STIs).[41,42] M184V or M184I mutations confer >1000-fold resistance to both lamivudine and emtricitabine.[27-31] Mutations M184V/I also decrease the susceptibility to abacavir and didanosine. M184V hypersensitizes HIV-1 to zidovudine and tenofovir, and exerts synergy with these drugs by altering RT's processivity among multitude of other effects.[43-48] Importantly, M184V impairs the replication capacity of mutant viruses in the presence of lamivudine, relative to wildtype viruses in the absence of therapy. M184V/I quickly dissapears after treatment suppression, decreasing to low-abundance populations, commonly undetected by bulk genotyping. However, the presence of M184V/I in any prior genotype testing must be interpreted as the persistence of that mutation, despite being undetected in current genotypes.

The TAM Pathways

Thymidine-analog resistance mutations (TAMs, at positions 41, 67, 70, 210, 215, and 219),[49,50] confer resistance to ZDV and d4T, and substantially contribute to ABC and ddI resistance.[51,52] There are two TAM pathways, TAM1 (41L, 210W, 215Y) and TAM2 (67N, 70R and 219E/Q), which can be mutually exclusive, particularly during early TAM accumulation. However, in clinical practice, overlap patterns are also common. The TAM1 pattern probably exerts stronger clinical cross-resistance to tenofovir than TAM2 in subtype B viruses.[53] In general, significant decreases in NRTI susceptibility require the stepwise accumulation of several resistance mutations.[5,34,49,54-61] Evolution along the TAM pathways leads to increasing resistance levels and extension of cross-resistance to all the currently existing NRTIs (Fig. 6.1.3).

Interestingly, although TAMs induce resistance to most NRTIs *in vivo*, viruses with TAMs have much smaller *in vitro* susceptibility decreases to abacavir, tenofovir or didanosine than to zidovudine. Indeed, susceptibility to didanosine as measured in tissue cell culture is often below the level of significance with early TAM patterns. This discrepancy between *in vivo* and *in vitro* data may be explained, on one hand because zidovudine is a larger molecule that could more easily be excised. On the other hand, ddI, ABC and TDF can escape excision by forming excision refractory closed complexes, which is facilitated by high concentrations of dNTPs. Because the tumor-derived cells used in HIV phenotypic assay systems contain high levels of dNTPs, it is possible that resistance in cells with lower dNTP pools (such as the natural target cells of HIV *in vivo*) may be significantly higher.

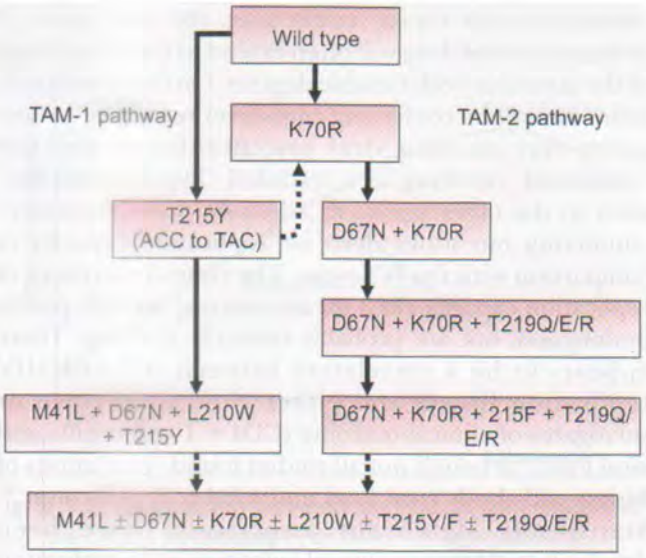


Fig. 6.1.3: Ordered accumulation of thymidine analog resistance mutations

The single point mutation at codon 70 (K65R) emerges first but confers relatively low-level ZDV resistance. Subsequently, the T215Y mutation emerges in different viral genomes and these viruses overgrow the K70R mutants. Because the T215Y substitution requires a double-nucleotide mutation (ACC to TAC), it would be expected to occur at a much lower frequency than that of the K70R point mutation, thus explaining its later emergence. Continued replication of partially resistant T215Y mutants in the setting of nonsuppressive regimens eventually results in the accumulation of the M41L, L210W, and D67N mutations. Alternatively, the D67N mutation arises in viruses already carrying a K70R mutation, with eventual accumulation of K219Q, K219E, or K219R substitution and the T215F substitution (which, like T215Y, requires a double mutation [ACC to TTC]). The poor replication kinetics and lower fitness of T215F compared to T215Y along with the modest advantage over the wild-type virus in the presence of ZDV most likely explain why this mutation rarely occurs as an initial ZDV resistance mutation or in association with M41L. If replication under thymidine analogues ensues, mixed TAM 1/2 patterns can emerge.

Source: Hu Z, Giguel F, Hatano H, Reid P, LuJ, and Kuritzkes DR. Fitness Comparison of Thymidine Analog Resistance Pathways in Human Immunodeficiency Virus Type 1. J Virol. 2006; 80(14): 7020-27.

The K65R and L74V mutations

This pathway affects susceptibility to tenofovir (TDF) and abacavir (ABC), and includes the K65R, L74V and Y115F mutations plus several accessory mutations (T69N/S/A,V75T), situated in a loop between the beta-2 and beta-3 strands in the "fingers" region of the RT.[62]

Mutation K65R is the signature mutation for TDF, although it also confers intermediate levels of resistance to ddI, ABC, 3TC, FTC, and low-level resistance to d4T.[62-71] K65R hypersensitizes HIV-1 to ZDV and does not develop in patients receiving ZDV-containing regimens.[66]

L74V occurs frequently during ddI and ABC monotherapy.[72] L74V is ddI's signature mutation, being sufficient to cause failure in patients receiving ddI monotherapy. ABC failure, in contrast, requires the accumulation of additional mutations.[73] As well, L74V hypersensitizes HIV-1 to ZDV and, less clearly, to d4T and TDF.

Mutations at position 69 are the most frequent substitutions in HIV-1 genotypes other than TAMs and M184V, and have been shown to contribute to resistance to every NRTI. V75T confers resistance to d4T, ddI and ddC, and generally occurs in the context of multinucleoside resistance.

The Q151M and 69 Insertion Complexes

A fourth, infrequent pathway includes multinucleoside resistance driven by the Q151M mutation and/or 69 insertions.[51,52,74,75] The Q151M complex is seen in less than 5 percent of all HIV strains with resistance to nucleoside analog. It is most often selected for in the course of the failure of regimens containing stavudine and didanosine, but can also be seen in subjects with prolonged ZDV exposure. Q151M is a two base-pair change in a conserved RT region that is close to the first nucleotide of the single-stranded nucleotide template. Q151M alone causes intermediate levels of resistance to ZDV, ddI, d4T, and ABC, but not to TDF. It is nearly always followed by mutations at positions 62, 75, 77, and 116. Such secondary mutations increase resistance and the activity of RT. Isolates with V75I, F77L, F116Y, and Q151M have high-level resistance to ZDV, ddI, d4T, and ABC, and low-level resistance to 3TC and TDF. Insertions in position 69 occur only in 2 percent of heavily pre-treated patients and confer high-level resistance to TDF and other NRTIs.

Non-nucleoside Analog

Resistance patterns are different for first and second generation NNRTIs.

First Generation NNRTIs: Nevirapine and Efavirenz

First-generation NNRTIs are characterized by having a low genetic barrier to attain resistance.[51,52] Mutations selected for after nevirapine or efavirenz failure are all located in the drug-binding pocket.[76-82] While most NNRTI resistance mutations affect residues that are directly involved in inhibitor binding, a few have been found to act indirectly, by changing the position or the orientation of the amino acids involved with direct contact with the inhibitor.

NNRTI resistance mutations can be divided into three separate clusters:

- Cluster 1: L100I, K103N, V106A and V108I
- Cluster 2: Y181C, Y188L/C/H , and G190S/A
- Cluster 3:P225H, M230L, and P236L.

The first two clusters represent two opposite sides of the NNRTI binding pocket of RT in the main subunit p66; the third cluster is carried by the second RT subunit, p51.

Because of subtle differences in the interaction between various NNRTIs and the hydrophobic pocket,[77] the mutations that emerge most frequently tend to be drug-dependent. Nevirapine resistance is often associated with the Y181C mutation, but other mutations, such as Y188C, K103N, G190A, and V106A, also occur. Given that Y181C increases HIV-1 susceptibility to ZDV,[82] Y181C mutants are selected against during nevirapine failure in the presence of ZDV, leading to the emergence of variants containing the K103N mutation. Initial resistance to efavirenz is generally characterized by the K103N mutation, but the Y188L and G190A/S mutations are also commonly seen.

All the above mentioned mutations generate cross-resistance to EFV and NVP. The K103N and Y188L mutations generate high-level phenotypic resistance to both drugs *in vitro*, whereas Y181C causes high-level resistance to NVP but only a two-fold decrease in phenotypic susceptibility to EFV *in vitro*. Nevertheless, clinical cross-resistance to EFV is evident, since subjects failing NVP with an Y181C virus and no K103N detectable are also more likely to fail EFV therapy than those with a WT virus. Sometimes, the presence of minority K103N mutants can partially explain the excess risk of virological failure.[83] Y181C mutants could also pre-exist in many subjects as minority variants. Previous reports noted the emergence of NNRTI resistant viruses (mostly Y181C mutants) within one week after the initiation of NVP when given alone or together with zidovudine.[82,84,85] It was calculated that minority Y181C mutants were present before therapy at a frequency of 7 and 133 per 10,000 copies of plasma HIV-1 RNA in two subjects in whom this mutation emerged during NVP therapy.[85]

In opposition to PI or NRTI-resistance mutations, NNRTI resistance mutations have a minimal impact on HIV's replication capacity,[79,80,86] so NNRTI maintenance is of little utility to impair viral virulence.

These data imply that sequential treatment with EFV and NVP or maintenance of any of these drugs in the presence of detectable viremia is not only futile, but could hamper the virological outcomes of a future treatment with etravirine through the accumulation of further

NNRTI resistance mutations. A recent EuroSIDA Study found that maintenance of NVP or EFV therapy in viremic subjects was associated with a rate of accumulation of NNRTI mutations of 1 every 2.2 years. Etravirine-specific mutations, however, accumulated more slowly (1 every 4 years), leading to an 8 percent mean reduction in etravirine activity per year. As expected, viruses with higher susceptibility to NNRTIs accumulated further NNRTI resistance mutations faster.[87]

The long plasma half-life of NVP and EFV ensures sufficient drug levels during continued treatment. This characteristic, however, becomes problematic when NNRTI treatment is interrupted. The slow decay of NVP or EFV plasma levels in comparison with that of the accompanying NRTIs or PIs often leads to periods of functional monotherapy characterized by suboptimal NNRTI levels in the presence of active replication, a situation that fuels NNRTI resistance evolution.

Second Generation NNRTIs: Etravirine

Etravirine (ETV) is a second generation NNRTI that retains antiviral activity against HIV-1 carrying the K103N mutation. Its potency appears to be related to etravirine's flexibility as a molecule. Etravirine is a diarylpyrimidine, a type of organic molecule with some conformational isomerism that can bind the enzyme reverse transcriptase in multiple conformations, allowing for a more robust interaction between etravirine and the enzyme, even in the presence of mutations.

Mutation Y181C confers a moderate decrease in susceptibility to ETV; the accumulation of other resistance-associated mutations (V90I, A98G, L100I, K101E/H/P, V106I, E138A, V179D/F/T, Y181C/I/V, G190S/A and M230L) is required to render HIV-1 highly resistant to this drug. The relative weight of the 17 known etravirine resistance mutations according to clinical outcome (Table 6.1.1) and phenotypic susceptibility (Table 6.1.2) correlates has been reported.[88-90]

In terms of interpretation of the relative weights of each mutation, the main differences between the two scores developed so far are that Tibotec-Jannsen® gives the highest weight to mutations Y181I/V and considers mutations A98G, V106I, G190A/S as clinically relevant. Also, mutation V179F is given a 1.5 weight although it was always found in combination with Y181C. In comparison, the score by Monogram Biosciences® considers mutations L100I, K101P, Y181C/I/V to be the most important and does not retain mutations A98G, V106I, G190A/S as being phenotypically relevant.

The lack of upper cut-off in the Monogram Biosciences,® score makes it difficult to ascertain residual antiviral activity of etravirine in the presence of multidrug resistant HIV. Finally, as with other NNRTIs, TAMs and M184V seem to increase the susceptibility to etravirine *in vitro*.[91]

Table 6.1.1: Weighted classification of etravirine resistance mutations by clinical outcome in the DUET Trials (Tibotec-Jannsen®)

Weight	*Mutations*
3	Y181I/V
2.5	K101P, L100I, Y181C, M230L
1.5	E138A, V106I, G190S, V179F*
1	V90I, V179D/T, K101E/H, A98G, G190A

**Always detected together with Y181C*

Interpretation

Weighted mutation score	*Response rates in DUET trials*
0–2	74% (highest response)
2.5–3.5	52% (intermediate response)
= or > 4	38% (reduced response)*

**comparable to the control arm*

Table 6.1.2: Weighted classification of etravirine resistance mutations by phenotypic susceptibility (Monogram Biosciences®)

Weight	*Mutations*
4	L100I, K101P, Y181C/I/V
3	E138A/G, V179E, G190Q, M230L, K238N
2	K101E, V106A, E138K, V179L, Y188L
1	V90I, K101H, V106M, E138Q, V179D/F/M, Y181F, V189I, G190E/T, H221Y, P225H, K238T

**Mutations not retained: A98G, V106I, G190A/S.*

Interpretation: A weighted score of 4 is equivalent with the lower clinical cutoff for etravirine (2.9) that defines reduced susceptibility. Mutations with a WF of 4 (L100I, K101P, and Y181C/I/V) are sufficient to confer reduced susceptibility to ETV on their own.

In summary, etravirine may remain effective after early virological failure to EFV or NVP-including regimens. Other diarylpyrimidine-analog like rilpivirine are currently being developed as potential anti-HIV agents. Etravirine hypersusceptibility is common in clinical practice. In the DUET studies, 34 percent of all samples displayed a FC<0.4 (Biological and clinical cut-off analysis or etravirine in the PhenoSense HIV assay. Coakley E, Chappey C, Benhamida J et al. Proceedings of the XVII International HIV Drug Resistance Workshop. Sitges, Spain. June 10-13, 2008. Abstract 122.). The clinical significance of this phenotypic hypersusceptibility to etravirine remains to be well defined.

Mutations in the Connection and RNAse H Domains of Reverse Transcriptase

It is still unclear if mutations in the RT's connection or RNAse H. domains affect the virological outcomes of therapy. These domains are not routinely investigated by commercial genotypic resistance assays; mutations in these regions usually remain undetected and are not incorporated in genotypic resistance scores or other interpretation systems.

Mutations in the connection and RNAse H domains of the RT are virtually absent in treatment naïve individuals, but can be co-selected on the same genome as TAMs, significantly increasing zidovudine resistance when combined with TAMs.[92-94] They also increase, although to a much lesser extent, cross-resistance to lamivudine, abacavir, and tenofovir but do not affect susceptibility to stavudine or didanosine.[95] Three mutations (N348I, T369I, and E399G/D) in the reverse transcriptase C-terminus are associated with the increased resistance to zidovudine and to NNRTIs. Mutation N348I decreases susceptibility to nevirapine 7.4-fold and efavirenz 2.5-fold and enhances NNRTI resistance in the context of K103N. This mutation is more likely to be selected with zidovudine and nevirapine treatment and may appear early after treatment failure, even preceding TAMs.[96]

In isolation, T369I reduced susceptibility to efavirenz and zidovudine 3 and 2.3-fold.[94] In combination with K103R/V179D T369I, N348I and E399D cause 13, 6, and 2.6-fold increased resistance, respectively, to efavirenz. The double mutant T369I/N348I causes fold-change of 11, 60 and 7 to efavirenz, nevirapine and zidovudine, respectively. Viruses containing T369I or N348I show reduced RTexpression, and those containing T369I, N348I or E399D show impaired processing of p55gag polyproteins.[94]

Mutation E399G increases efavirenz resistance 3.6-fold and reduces viral replication capacity when associated with other mutations in the NNRTI binding pocket (L100I, V106I, V179D, and F227C). Mutations in the C-domain could modulate NNRTI resistance by affecting dimerization of p66/p51 heterodimers[97] or slowing the RNAseH processivity, thus allowing more time for primer excision to occur.

The clinical utility of detecting mutations in the connection or RNAseH domains will depend on (a) whether these mutations are early markers of the future TAMs accumulation, and (b) the extent to which they reduce susceptibility to NNRTIs, particularly etravirine.

Protease Inhibitors

The substrate-binding domain of the protease is a symmetrical cavity delimited on both sides by the two subunits of the dimer.[3] The "floor" of the cavity contains two aspartic residues at position 25 that are essential for the proteolytic cleavage reaction. The "roof" of the cavity is formed by two mobile flaps, which open when the cavity is empty and close when it becomes occupied by its natural substrate or an inhibitor.[3] The overall shape and chemical properties of the cavity, as well as the mobility of the flap are important for proper substrate recognition, binding and cleavage.[6,98,99]

Protease inhibitors (PI) have been designed to fit the cavity very tightly, based on the precise knowledge of its 3-D structure.[99] Therefore, substitutions of amino acids in direct contact with the inhibitor or of distant aminoacids that modify the overall shape of the cavity, will both be able to disrupt fitting of the PI within the cavity and induce resistance.[3,6,98,99]

Most PI resistance mutations appear to enlarge the size of the substrate-binding cavity. Usually, PIs occupy more space in the substrate-binding cavity than the natural protease substrates. Such natural substrates require sequential and ordered cleavage, which implies less tight interactions with the protease and less efficient cleavage from this enzyme. Therefore, the development of PI resistance only impairs Gag and Gag-Pol cleavage slightly, and synthesis of mature virions can continue.

Mutations in Gag or Gag-Pol can also induce PI resistance, particularly in the presence of resistance mutations in protease.[1] The primary function of Gag cleavage site mutations, however, is to partially compensate for the loss of cleavage by the protease at these sites. Thus, Gag-Pol mutations usually restore the fitness defect induced by protease mutations.

Each PI is associated with its own "major" or signature mutations. When unboosted PI were used, every "major" mutations usually conferred moderate-to-high resistance to a specific PI. With the high pharmacological barrier to resistance of the current boosted PI, this is not so clear. Persistent viral replication under PI therapy leads to the accumulation of additional major and minor mutations that increase cross-resistance to other PIs and compensate for fitness reductions derived from major mutations.[1,100] Each individual PI mutation tends to have a small impact of virus susceptibility *in vitro;* some "secondary" mutations may cause larger decreases in susceptibility than major PI resistance mutations.[3] When a specific score or list of mutations that confer resistance to a PI has been identified, actually every mutation induces a steady decrease in the rate of virological suppression with that PI.

Protease inhibitor-naïve subjects who experience virologic failure of a ritonavir-boosted PI regimen systematically lack major PI resistance mutations and do not induce phenotypic resistance to the PI used. Furthermore, they have less NRTI resistance mutations than with non-boosted PIs. Thus, subjects with virological failure to boosted-PIs without baseline protease resistance have noncompliance to treatment, and can only accumulate M184V/I and occasionally further NRTI mutations. They should be switched to new antiretroviral regimens including three active drugs, usually with new NRTIs, in a regimen based in a boosted PI or a first-generation NNRTI.[101-108] The early use of CCR5 antagonists or raltegravir is very attractive when 3 active

drugs can not be completed with only NRTIs, NNRTIs and PIs.

Saquinavir Resistance

Saquinavir's signature mutations are G48V and L90M. Each mutation results in a 3- to 10-fold decrease in susceptibility; viruses with both mutations have more than 100-fold decreased susceptibility.[109-111] The G48V mutation appears first *in vitro*, but L90M is the most frequent *in vivo*. *In vivo*, the G48V mutation is frequently found alongside V82A mutation,[109, 110] which confers cross-PI resistance. The L90M mutation reduces susceptibility to most other PIs, particularly to nelfinavir. As with other PIs, saquinavir resistance mutations are much less frequent when this drug is given alongside ritonavir boosting.[100]

Indinavir Resistance

Indinavir is a potent but highly toxic PI rarely used nowadays because of its poor tolerability. Major mutations include M46I, V82A/F/T, and I84V.[10] Amino acid substitutions at positions 10, 20, 24, 54, 63, 64, 71, and 90 in PR are also associated with resistance *in vivo*. The number of mutations predicts the degree of resistance. Mutations M46L/I and V82A are the first to occur during indinavir failure, followed by I54V or A71V/T.[112] Indinavir-associated mutations induce broad cross-resistance to ritonavir, amprenavir, lopinavir/ritonavir, and tipranavir being major mutations for these PIs; they also decrease susceptibility to saquinavir, nelfinavir, and atazanavir. The accumulation of a minimum of 4 substitutions in protease (M46I, L63P, V82T, and I84V) confers resistance to most PIs.[10]

Ritonavir Resistance

Today, ritonavir is only used as a pharmacokinetic enhancer because of its capacity to potently inhibit different cytochrome P450 isoenzymes. The I84V substitution is the major determinant of ritonavir resistance. The addition of the V82F mutation significantly increases resistance to ritonavir but impairs the replication capacity of the double mutants. Additional M46I, L63P, and A71V mutations improve replication capacity. Importantly, patients with rebound viremia while on ritonavir typically accumulate resistance mutations in the following: V82F → M36I, I54V, A71V→I84V, L90M.[4,7]

In vitro, ritonavir-resistant strains including either the single mutations I84V or V82F or the combination of the 4 mutations M46I, A71V, V82F, and I84V displayed similar levels of resistance to ritonavir and indinavir, but only a slight reduction in susceptibility to saquinavir.[9,10] However, the triple mutants including M46I, L63P, and I84A have an 80-fold increased IC_{50} for ritonavir, saquinavir, and indinavir, and a 125-fold increased IC_{50} for nelfinavir.

Nelfinavir Resistance

On the June 6th, 2007 both the Medicines and Healthcare products Regulatory Agency and the European Medicines Agency (EMEA) released an alert requesting the recall of any of the drug in circulation because of fears that batches of the therapy may have been contaminated with potentially cancer-causing chemicals. Research is ongoing to try to reposition this drug as an anti-cancer agent.

For subjects who took nelfinavir in the past, it is interesting to remember that nelfinavir-resistant viruses often preserve sensitivity to other PIs. The D30N mutation is the first to appear during nelfinavir failure in patients infected with subtype B HIV; L90M is the first mutation in non-subtype B HIV-1 infected subjects. The D30N mutation confers high-level nelfinavir resistance *in vitro* (>30-fold increase in IC_{50}), but also impairs replication capacity[113] to the extent of constraining the accumulation of additional mutations. Occasionally, substitutions at positions 36, 46, 71, 88 can be found alongside D30N. The D30N mutation does not reduce susceptibility to other PIs. Indeed, mutation N88S can cause hypersusceptibility to amprenavir *in vitro*.[114,115]

The L90M mutation is the signature mutation in non-subtype B HIV-1, but can also emerge in subtype B viruses in the face of persistent viremia under nelfinavir exposure. L90M is often associated with other minor mutations that confer cross-resistance to other PIs, especially to saquinavir, ritonavir, indinavir, tipranavir, and lopinavir/ritonavir, but also to amprenavir and atazanavir.

Amprenavir and Fosamprenavir Resistance

Amprenavir has been replaced by its calcium phosphate ester prodrug, fosamprenavir, which has a much more favorable pharmacokinetic profile, reduced pill burden, and no food interactions. However, fosamprenavir is quickly hydrolyzed in the gut to produce the active compound amprenavir and virtually no fosamprenavir reaches the bloodstream. Therefore, the resistance profile of both drugs is superimposable. Ritonavir boosting of fosamprenavir, however, decreases the frequency of resistance mutations.[100]

Patients with early virologic failure to amprenavir often lack genotypic or phenotypic evidence of cross-resistance to other PIs *in vitro*, although low-level cross-resistance to ritonavir and lopinavir is sometimes noted.[116] On the other hand, many patients with virologic failure to other PIs may remain susceptible to amprenavir.[117]

The signature resistance mutation for amprenavir is I50V,[118] which is rare after virological failure to most PIs. It appears early after amprenavir failure and, as a single mutation, confers 2- to 3-fold decreased susceptibility to amprenavir. However, I50V confers low fitness, so acquisition of high-level resistance to amprenavir sometimes requires additional substitutions in Gag.[119-121] Of note,

I50V is associated with the greatest reduction in darunavir susceptibility but increases viral susceptibility to tipranavir.[104]

The second amprenavir signature mutation is I84V, although it is less common than I50V, I54L/M, or the V32I + I47V combination.[122] Mutation I84V is associated with reduced susceptibility to all the PIs (lopinavir, indinavir, nelfinavir, ritonavir, saquinavir, and tipranavir), and its selection should be avoided if at all possible.[123,124] The addition of V82F to I84V significantly increases resistance to ritonavir, indinavir, nelfinavir, and amprenavir.[125]

Mutations I54L/M and/or the combination V32I + I47V are often seen in patients failing ritonavir-boosted amprenavir, but they usually appear in patients with further experience to PIs.[126] I54L/M and V32I + I47V reduce the virologic response to ritonavir-amprenavir[127] and confer cross-resistance to other PIs.

In addition to the four main pathways of amprenavir resistance, namely I50V, I54L/M, V32I + I47V, and I84V, multiple accessory mutations are also associated with resistance to amprenavir *in vivo*, including substitutions at residues 10, 32, 46, 47, 54, 73, and 90.[122] Significant resistance to amprenavir can be predicted when one of the following combinations of mutations is encountered:

1. I84V alone.
2. I50V plus one or two mutations of the following group: L10F/I/R/V, V32I, M46I/L, I54L/V, V82I/F, or L90M.
3. Three or more mutations of the above listed group (L10F/I/R/V, V32I, M46I/L, I54L/V, V82I/F, or L90M).

Finally, mutations K20T and N88S[128,129] and the atazanavir-related mutation I50L[130] have been associated with hypersusceptibility to amprenavir and other PIs, particularly when other resistant mutations are present.

The specific mutational pathways observed at first failure of unboosted fosamprenavir bid are either the I54L/M mutation or the V32I plus I47V mutations. The I50V mutation can emerge if fosamprenavir is continued in the presence of ongoing viral replication. Other major fosamprenavir mutations include I54M, L76V and I84V.[131-135] The accessory mutations L33F and to a lesser extent V11I and L89V are associated with decreased fosamprenavir susceptibility.[135-137] Finally, mutations M46I/L, I54V/A/T/S, V82A/T/F/S, and L90M rarely occur during fosamprenavir failure, but are common with other PIs and can confer low-to-intermediate cross-resistance to this drug. N88S increases fosamprenavir susceptibility *in vitro* and *in vivo*.[138,139]

Lopinavir/ritonavir Resistance

Resistance to lopinavir/ritonavir can develop through two different pathways:[140,141] One resembles the indinavir pathway, with mutations M46I/L, I54V/T/A/S, and V82A/T/F/S.[123] The second is similar to the amprenavir resistance profile and includes mutations V32I, I47V/A, I50V, I54L/M and L76V.[135,142-144]

Mutations at position 82 reduce susceptibility approximately 2-fold. Mutations at positions 54 + 82 reduce susceptibility approximately 10-fold. The combination of mutations at positions 46, 54, and 82 together with accessory mutations at positions 10 and 20, reduces LPV susceptibility >50-fold and reduce the virologic response to LPV/r salvage therapy.[123,142,145,146]

I47V and less commonly I47A are selected during LPV/r salvage therapy.[135,144] I47A is a rare mutation which occurs in combination with V32I in which case it reduces LPV susceptibility >50-fold.[147-149] L76V, an uncommon mutation, is selected by and is associated with decreased LPV susceptibility.[142,143]

The accessory mutations L24I and F53L have been associated with reduced LPV susceptibility.[123] L33F is selected during LPV salvage therapy and associated with reduced LPV susceptibility and virological response.[150]

Mutations I84V and L90M acquired during virological failure to other PIs, each reduce LPV susceptibility approximately 2-fold and can contribute to higher levels of resistance when associated with other LPV-resistance mutations. Both mutations appear to reduce susceptibility to LPV less than that of other PIs except darunavir. G48V is not selected by LPV but has been associated with decreased virological response in a large multivariate analysis.[150] G48M and I84A/C are rare mutations associated with high-levels of resistance to multiple PIs including LPV.[140]

Atazanavir Resistance

Atazanavir is a semisymmetrical azapeptide PI that has shown equal potency to efavirenz in antiretroviral-naive patients and, when boosted with ritonavir, is as efficacious as lopinavir/ritonavir in antiretroviral naïve patients.[103] When used without ritonavir as the initial PI, atazanavir selects for the I50L mutation; this signature mutation for atazanavir differs from the I50V mutation seen with amprenavir. I50L occurs less frequently in patients receiving atazanavir/ritonavir or in previously PI-treated patients receiving atazanavir.[151,152] The I50L mutation produces a significant reduction in susceptibility to atazanavir but has been associated with increased susceptibility to other PIs. In initial PI failure, atazanavir may select for the A71V mutation together with I50L, which increases atazanavir resistance but diminishes viral fitness. When used in PI-experienced patients or when combined with saquinavir, atazanavir can select for the I84V mutation and, less frequently, for the I54L mutation. Whereas the I50L mutation does not confer cross-resistance to other PIs, the I84V mutation confers broad PI cross-resistance. Moreover, the I54L is a major darunavir resistance mutation. In vitro, atazanavir selects

for V32I, M46I, I84V and N88S. Classical PI mutations, such as V82A and L90M, have been shown to confer cross-resistance to atazanavir, particularly when present in combination with each other or with other known PI resistance mutations (V32I, G48V/M, F53L, I54V/L/M/T/A, G73S/C/T/A and I84V/A/C). However, as with many PI-based regimens, in patients who are naive to PIs, the most common resistance profile observed with early atazanavir failure is wild-type virus.

Tipranavir Resistance

Tipranavir is a sulfonamide-containing dihydropyridone. It is metabolized by the cytochrome P450 system and, while ritonavir coadministration increases its exposure, tipranavir in turn markedly increases ritonavir metabolism, necessitating use of ritonavir 200 mg twice daily when boosting tipranavir in PI-experienced patients. The major tipranavir-associated mutations are V32I, I47V, I54V/A/M, V82L/T and I84V. Mutations V82L/T and I84V have been the most common major PI-resistance mutations to emerge during tipranavir/ritonavir salvage therapy.[153] Whereas V82L occurs in viruses that were wildtype at baseline, mutation V82T develops mostly in viruses with the V82A substitution at baseline.[154] Mutations V82L/T are associated with the greatest decreases in tipranavir susceptibility *in vitro*. In addition, I47V, I54A/V/S/M, I84V have also been associated with reduced TPV susceptibility.[154, 155] The accessory mutations L33F/I are among the most commonly occurring substitutions to emerge during tipranavir/ritonavir treatment and are associated with decreased virologic response when combined with other major mutations. E35G, K43T, Q58E, T74P, N83D and L89V are nonpolymorphic mutations that have been associated with decreased virologic response to tipranavir/ritonavir in multivariate analyses.[153,155]

Importantly, mutations L24I, I50V, I50L, I54L, and L76V are associated with increased tipranavir susceptibility. This effect is particularly large for I50V/L and I54L.

Different algorithms have been developed for tipranavir. The most comprehensive and better performing one was developed by independent investigators together with its manufacturer using the data from the RESIST trials[156] to predict virologic response (Table 6.1.3). A few existing TPV score mutations, most of which are uncommon in patients who have not used TPV, had the greatest weights (47V, 54A/M/V, 58E, 74P, 82L/T, 83D) while the others were considered minor or not important in terms of accurately predicting virologic response. The score also included mutations associated with increased susceptibility to tipranavir (24I, 50L/V, 54L, 76V). These mutations remained in the final score with large negative weights. Tested on an independent dataset against other commonly used scores, the new weighted score compared favorably, showing a better prediction than the unweighted score.

Darunavir Resistance

The major darunavir-associated resistance mutations are V11I, V32I, L33F, I47V, I50V, I54L/M, L74P, L76V, I84V, and L89V. In an analysis of pooled week 24 data from POWER 1, 2, and 3 studies using darunavir/ritonavir 600/100 mg bid (N = 458), baseline darunavir fold change in IC_{50} was a strong predictor of virological response at week 24.[104] Preliminary phenotypic clinical cut-offs of 10 and 40 were established. Protease mutations associated with diminished darunavir/r virological response were V11I, V32I, L33F, I47V, I50V, I54L/M, G73S, L76V, I84V, and L89V (darunavir RAMs). These mutations occurred in the presence of a high number of other PI resistance mutations. About 60 percent with 0, 45 percent with 1-2, and ≤ 20 percent with ≥ 3 darunavir RAMs had RNA <50 copies/ml at week 24. A diminished response to darunavir/ritonavir was also observed in the presence of ≥ 14 PI resistance mutations other than the darunavir RAMs. The fold-change decrease in darunavir susceptibility is summarized in Table 6.1.4. Mutations developing during darunavir/r virological failure were V32I, L33F, I47V, I54L, and L89V. In phenotypic studies,

Table 6.1.3: Weighted classification of tipranavir mutations

Class	Classification by weight	Mutations (weight of each mutation)
Increased response	<0	24I (-2), 50L/V (−4), 54L (−7), 76V (−2)
Minor mutations	1-2	10V (+1), 36I (+2), 43T (+2), 46L (+1), 84V (+2)
Major mutations	>2	47V (+6), 54A/M/V (+3), 58E (+5), 74P (+6), 82L/T (+5), 83D (+4)

Interpretation

Weighted mutation score	Interpretation based on RESIST trials
< or 3	Susceptible
>3 and ≤ 10	Partially susceptible
>10	Resistant

Table 6.1.4. Weighted classification of darunavir mutations based on fold-change in IC_{50} *in vitro*

Fold-change	*Mutations*
>4	50V
3-4	54M, 76V, 84V
2-3	32I, 33F, 47V, 74P*
<2	11I, 54L, 89V

* in some studies, mutation 74P is associated with a fold-change comparable to that of I50V. *Interpretation:* Diminished response to darunavir when 3 or more of these mutations were present at baseline

I50V, I54M, L76V, and I84V reduced susceptibility to the greatest extent. V32I emerged in 30 percent of failures according to prescribing information. Of note, mutation I50V is associated with the largest susceptibility loss to darunavir in vitro but it hypersensitizes the virus to tipranavir. Other mutations that increase susceptibility to tipranavir are D30N, 41K, G48V, I50L, 53L/W/Y, I54L, H69K, 12S, 61K, N88S, and 76V.

In a larger follow-up study, which also included the DUET studies, all of the mutations with the exception of G73S were confirmed and T74P was added as a predictor of decreased virological response.[104] In an independent study, V32I, L33F, and I47VA were found to be associated with decreased virological response to DRV/r salvage therapy.[157] In addition to the seven major PI-resistance mutations, mutations V11I, L33F, G73S/T/C and L89V were associated with a decreased virological response to DRV/r in the POWER and DUET studies.[104]

Finally, although mutation V82F has not been reported to develop in viruses from patients receiving DRV/r it has had a major effect on DRV/r susceptibility in multivariate analyses of the mutations present in DRV/r resistant virus isolates.[158]

Combined Effect of Etravirine and Darunavir Resistance Mutations

Because darunavir is often given together with etravirine as salvage therapy, it is important to estimate the response rates to these two drugs in the presence of combined resistance mutation patterns. In a pooled subgroup analysis of week 24 data from DUET-1 and DUET-2 trials,[159] favorable combined etravirine and darunavir resistance profiles predicted higher virologic response in multiclass-experienced patients receiving etravirine plus darunavir/ritonavir together with optimized NRTIs but without *de novo* enfuvirtide. The highest response rates were seen in patients with etravirine FC ≤3 and darunavir FC ≤40. There were high response rates in patients with no etravirine RAMs and ≤3 darunavir RAMs and in patients with a total of ≤3 combined etravirine plus darunavir RAMs. In addition, there were also high responses rates in patients with weighted etravirine genotypic score ≤2 with ≤3 darunavir RAMs, and those with weighted etravirine genotypic score ≤3.5 with ≤1 darunavir RAMs.[160]

Integrase Inhibitors

Raltegravir (formerly MK-518) is an hydroxypyrimidinone carboxamide derivative of the diketobutanoic acid family approved by the FDA and the EMEA for treating, in combination with other antiretroviral drugs, treatment-experienced HIV-1 infected adult patients. Studies are on their way to assess the role of raltegravir in first-line therapy. By the time of finishing this review, elvitegravir (GS-9137) was still in Phase II of development, although Phase III trials were expected to begin shortly. It is likely that elvitegravir will be positioned similarly to raltegravir in antiretroviral therapy schedules. Cumulative data, however, indicate that there is extensive cross-resistance between the two drugs. Another integrase inhibitor currently in late development, GSK1349572, with an unprecedented antiviral activity, has a unique resistance profile and limited cross-resistance to raltegravir and elvitegravir [J. Lalezari, L. Sloan, E. Dejesus, et al, for the ING111521 Investigators. Potent antiviral activity of S/GSK1349572, a next generation integrase inhibitor (INI), in INI-naïve HIV-1 infected patients. 5th IAS Conference on HIV Pathogenesis Treatment and Prevention 2009 Cape Town (Abstract TUAB105)].

The need for ritonavir boosting of elvitegravir (raltegravir is eliminated through glucuronidation, so does not require ritonavir boosting) may also imply differential toxicity patterns that may affect their relative positioning in HIV therapy.

Integration is a multistep process that occurs in discrete biochemical stages: (i) assembly of a stable complex with specific DNA sequences at the end of the HIV-1 long terminal repeat (LTR) regions, (ii) endonucleolytic processing of the viral DNA to remove the terminal dinucleotide from each 3' end, and (iii) strand transfer in which the viral DNA 3' ends are covalently linked to the cellular (target) DNA. Each of the catalytic reactions (3' processing and strand transfer) is metal-dependent and requires integrase to be appropriately assembled on a specific viral DNA donor substrate. A DDE motif in the integrase catalytic site coordinates the interaction of the enzyme with two magnesium ions. The acidic moiety of raltegravir and elvitegravir inhibit is essential for inhibition and confers distinct metal-dependent properties on the inhibitor.[161] Binding requires divalent metal and resistance is metal dependent with active site mutants displaying resistance only when the enzymes are evaluated in the context of Mg(2+). The mechanism of action of these inhibitors is therefore likely a consequence of the interaction between

the acid moiety and metal ion(s) in the integrase active site, resulting in a functional sequestration of the critical metal cofactor(s).[162]

Resistance to raltegravir (RAL) evolves through at least three separate pathways defined by the signature mutations Q148H/K/R, N155H and Y143C/R.[163] These mutations impair viral replication to different extents. Mutations in residue 148 and N155H confer 10- to 25-fold, respectively, decreased susceptibility to raltegravir. Mutation Q148H is the one associated with greatest reductions in replication capacity. Accessory or secondary mutations accumulate to compensate for replication capacity losses (G140S in the presence of Q148H), or to further decrease viral susceptibility to raltegravir. Mutations L74M, E92Q, T97A, E138K, V151I, G163G/R, and D232D/N may also be present in raltegravir virologic failures. These secondary mutations by themselves contribute only in a modest way to resistance to raltegravir. However, when combined with either of the primary mutations N155H or Q148R/H/K, they lead to substantial further decreases in raltegravir susceptibility. The continued accumulation of resistance mutations in the absence of major fitness variations *in vivo*, suggests that raltegravir retains residual antiviral efficacy on viruses with major resistance mutations.

Mutations frequently encountered in the N155H pathway include E92Q, V151I, T97A, G163K and L64M. The most frequent secondary mutations in the Q148K/R/H pathways are G140A/S and E138K. Mutation G140S restores the fitness cost of Q148H. This combination of mutations is associated with the greatest susceptibility loss to RAL. The Y143C/R pathway is being characterized.

Development of resistance to raltegravir *in vivo* seems to be an ordered, stepwise phenomenon. Mutation N155H seems to emerge early in subjects failing raltegravir. In the presence of continued viral replication in the presence of raltegravir, this mutation is then replaced by Q148H, the fitness cost of which is compensated by the accumulation of G140S. Studies are undergoing to understand the mechanisms of these *in vivo* findings.

Mutations Q148H/K/R and N155H also confer resistance to elvitegravir (ELV). The E92Q mutation is probably a signature mutation for ELV, although it can also develop under RAL treatment. Recently, the L68V/I mutation was reported to increase resistance to both RAL and ELV in the presence of the other resistance mutations. The most frequent mutations found after elvitegravir failure in a phase IIb trial[164] were: E92Q, E138K, Q148R/K/H and N155H (each observed in 39% of subjects); S147G (32%); and T66I/A/K (18%). Viruses of subjects experiencing virologic failure in this study showed a mean increase in IC_{50} value of greater than 151-fold for elvitegravir and greater than 28-fold for raltegravir compared with control, further confirming the extent of cross-resistance between these two compounds.

Fusion Inhibitors

Enfuvirtide (T-20) is the only fusion inhibitor currently available in clinical practice. The clinical use of this drug is limited to deep salvage therapy, when no other treatment options are available, because it requires twice daily subcutaneous administration that is almost invariably associated with local adverse reactions at the puncture sites.

Development of enfuvirtide resistance is associated with changes in a conserved amino acid triad (GIV) at positions 36–38 and in aminoacids 39-45 in the HR1 region of gp41.[165,166] Regions associated with co-receptor specificity and susceptibility to enfuvirtide, such as the V3 loop of gp120 do not play a primary role in the development of clinical resistance to enfuvirtide.[167]

A variety of different mutations has been noted in the amino acid region 36–45 (Table 6.1.5), each conferring a distinct level of resistance or susceptibility to enfuvirtide in a defined molecular background. Enfuvirtide is a drug with low genetic barrier to attain resistance. Single amino acid substitutions in this region are the most common and cause variable degrees of susceptibility loss. Serial mutations, where the reversion of the primary mutation coincides with the generation of the second, are also known. Single substitutions exhibit a 5- to 10-fold reduction in susceptibility to enfuvirtide.[165] Double amino acid substitutions have been associated with the highest levels of resistance.[165] In addition, considerable differences in enfuvirtide IC_{50} have been observed between primary isolates bearing the same pattern of mutations in gp41 as well as differences between viruses isolated from patients enrolled in Phase II clinical trials and site-directed mutants bearing the same mutations (e.g. G36S/L44M). This suggests that other viral factors (e.g. the V3 loop, or the HR2 region) may modulate the sensitivity of the gp41 36–45 amino acid core region.[166-168] Mutations in the HR2 region (N126K and S138A), can also contribute to enfuvirtide resistance.[169]

Because amino acids 36–45 in the HR1 region of gp41 are highly conserved, mutations in this region are invariably associated with a fitness cost to the virus.[170] In the absence of drug, wild-type virus was able to replicate with faster kinetics than viruses bearing mutations. Within amino acids 36–38 of HR1 a relative order of GIV > DIV > DTV > DIM > SIM was found for the replication kinetics of mutant clones in the absence of drug. This relative order of fitness was reversed in the presence of enfuvirtide.[170] Viruses with double amino acid substitutions were less fit than those with single substitutions.

One consequence of the development of enfuvirtide-resistant mutants with attendant reduced fitness is that

Table 6.1.5. Enfuvirtide susceptibility of HIV-1 mutants carrying single and double substitutions in gp41 amino acids 36–45[167]

Substitution(s)[a]	Enfuvirtide EC50 (mg/l)	Enfuvirtide fold change[b]
NL4-3G[c]	0.012	
G36D	0.091	8
G36S	0.088	7
V38A	0.188	16
Q40H	0.256	21
N42T	0.045	4
N42E	0.015	1
N42S	0.006	1
N43D	0.210	18
N43S	0.067	6
N43K	0.063	5
L44M	0.021	2
L45M	0.017	1
G36S + L44M	0.181	15
N42T + N43K	0.388	32
N42T + N43S	0.727	61
V38A + N42D	1.685	140
V38A + N42T	1.782	149
V38E + N42S	6.156	513

[a] Relative to a consensus wild-type sequence of GIVQQQNNLL (NL4-3G).

[b] Relative to NL4-3G.

[c] NL4-3 altered to match the consensus sequence at amino acid position 36 (aspartic acid replaced by glycine).

Source: Michael L. Greenberg and Nick Cammack. Resistance to enfuvirtide, the first HIV fusion inhibitor. Journal of Antimicrobial Chemotherapy 2004 54(2):333-40; doi:10.1093/jac/dkh330

following discontinuation of enfuvirtide, wild-type virus has been found to outgrow resistant virus, restoring replicative capacity associated with normal drug susceptibility.[171]

In a study assessing the proportion of plasma virus carrying the V38A mutation in gp41 by allele-specific PCR in serial samples collected from 3 subjects who interrupted enfuvirtide, we demonstrated *in vivo* fitness differences for mutant versus wild type ranging from 25 to 65 percent in the absence of drug. The V38A mutant virus reemerged rapidly (within 1-2 weeks) during a subsequent enfuvirtide pulse, confirming that enfuvirtide resistance remains archived in the viral quasispecies and is ready to emerge very soon after re-exposure.

CCR5 Antagonists

The dominant pathway to virological failure to CCR5 antagonist therapy *in vivo* is a shift from CCR5 to CXCR4 use. Such shifts have been seen in 55 percent of subjects included in the MOTIVATE-1 and 2 trials[172,173] (maraviroc in treatment-experienced subjects), 35 percent of individuals in the ACTG A5211 trial[174] (vicriviroc in treatment-experienced patients) and in 31 percent of subjects in the MERIT study[175] (maraviroc as first-line therapy in antiretroviral-naïve individuals). Different analyses suggest that X4 viruses emerging during virological failure to CCR5 antagonists originate from pre-existing minority viral populations.[176]

Most maraviroc or vicriviroc-resistant viruses described to date, both *in vivo* and *in vitro*, contained mutations in the V3-loop stem. Maraviroc-resistant HIV-1 variants were generated by serial passage in vitro and have heterogeneous patterns.[177] Two mutations in the V3 loop, T316A and V323I, were associated with maraviroc resistance; a third V3 loop mutation, A319S, was not consistently observed. The effect of such resistance mutations, however, is dependent on the remaining envelope context. The same mutations that confer CCR5 antagonist resistance in one subject may not affect viral susceptibility in a different envelope background. Thus, unlike resistance to reverse transcriptase and protease inhibitors, resistance to small-molecule CCR5 antagonists may not result in the selection of stereotypical mutations.[178] Rather, the selected mutations may lead to env-specific structural changes that allow gp120 to adapt to an inhibitor-bound conformation of CCR5. The effect of such mutations is context-dependent.

The multiple conformations of CCR5 that exist *in vivo*, as for any allosteric protein, may also contribute to the variety of CCR5-inhibitor resistance mutations observed to date. Small-molecule antagonists may bind to several different conformations of CCR5. The emergence of a variety of seemingly unrelated mutations could, in the context of a particular envelope molecule, give rise to common structural changes that improve the efficiency of HIV-1 fusion and viral entry into target cells.

Resistant viruses acquire the ability to recognize receptor conformations stabilized by maraviroc and therefore can no longer be inhibited even at high compound concentrations. Thus, the HIV-1 virus can then bind to the CCR5 coreceptor despite this being occupied by maraviroc or vicriviroc. Phenotypically, this is evidenced by decreases in the percent maximal inhibition in resistant viruses relative to control, instead of right shifts in the IC_{50} curves.[179] Plateaus in dose–response curves are obtained with viruses that recognize both compound-free and compound-bound forms of the receptor.[179] The association between emergence of clinical resistance to maraviroc and plateaus in maximum inhibition or shifts in dose response is currently under investigation.

It was also seen that CCR5 antagonist resistance mutations confer a fitness cost to the virus in the absence of drug.[180] The extent of cross-resistance within the class is not yet known.

The phase IIb study of the CCR5 antagonist vicriviroc (ACTG A5211) studied 29 subjects with virologic failure from vicriviroc and identified one individual with HIV-1 subtype C who developed vicriviroc resistance.[180] Studies with chimeric envelopes demonstrated that changes within the V3 loop were sufficient to confer vicriviroc resistance. Resistant virus showed vicriviroc-enhanced replication, cross-resistance to another CCR5 antagonist, TAK779, and increased sensitivity to aminooxypentane-RANTES and the CCR5 monoclonal antibody HGS004. Pretreatment V3 loop sequences reemerged following vicriviroc discontinuation, implying a fitness cost of vicriviroc resistance mutations to the virus.[180]

Conclusion

Antiretroviral drug resistance is a complex but key issue in the clinical management of HIV infected individuals, as well as a public health problem, since HIV-1 resistance can be transmitted. Careful evaluation of resistance patterns is key to ensure enduring efficacy of antiretroviral therapy and widespread extension of its clinical benefits.

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6.2

Psychosocial Issues in Children Infected/Affected with HIV

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Introduction

Everyday around the globe, more than 1100 children under the age of 15 are infected with HIV, with the majority of these cases occurring due to mother to child transmission via pregnancy, birth, or breastfeeding. While the diagnosis of HIV once meant certain death, advances in medical treatment, such as the advent of highly active antiretroviral therapy (HAART), have had a dramatic impact on the outcome of perinatally or transfusion acquired human immunodeficiency virus type 1 (HIV-1) infection in children in developed nations.[1] As increasing numbers of these children are surviving into adolescence and young adulthood, the management of concomitant psychosocial issues has become increasingly important.[2]

Psychosocial and psychiatric management of HIV infected children and adolescents have evolved from a bereavement and family stabilization model to a quality of life in chronic illness model. While the medical management of HIV infection remains important, preparing for long-term survival, academic success, independent living, and prevention of secondary infection have become primary goals in the care of HIV infected youth. For most HIV infected young persons and their caregivers, complex social and psychiatric needs influenced by familial substance abuse, histories of trauma and family disruption, mental illness, socioeconomic stressors, and urban violence further complicate provision of care. This chapter provides a window into the psychosocial needs of this population by focusing on the critical milestones and challenges in the disease process. These include diagnosis disclosure, adherence, transition, testing, and end-of-life care. In addition, concomitant difficulties in youth infected with HIV, including anticipatory, complicated, and normal grief, cognitive impairment, psychosocial issues, and psychopathology will be reviewed. Issues relevant to HIV affected individuals (e.g. siblings or noninfected caregivers) will be briefly discussed.

Disclosure

Regardless of when and from whom disclosure occurs, it can be a highly stressful experience for all involved. Disclosure of a child's HIV status is not a singular event, but rather an ongoing process that sets off a cascade of continued disclosure as the child matures and engages in his or her own peer and romantic relationships. Depending on how disclosure is handled, it can set the stage for either a healthy approach to privacy, confidentiality, and social support, or can compound repeated traumatic events throughout the child's development.[1]

Disclosure by Caregivers to Children

One of the greatest areas of psychological stress for parents and caregivers is the question of when and how to disclose the HIV diagnosis to one's child.[1] The management of disclosure is a crucial component of medical, psychological, and social care.[3,4] Even though much more is now understood about the transmission of HIV than when AIDS was first reported, most families still keep the diagnosis a closely guarded secret. Parents may choose not to disclose the diagnosis to their children for a number of reasons, including a fear of the psychological affect that disclosure might have on non-infected siblings, the concern that the infected child will not keep the information confidential, or a belief that disclosing the illness to the child will bring an end to his innocence and will introduce him to a life of rejection and ostracism, and ensuing depression.[2,5] In addition, revealing a child's diagnosis often means disclosing other family secrets, including paternity of the child, and history of parental sexual behavior and substance use.[4] The fact that the majority of children acquired the virus from their mothers and that there is ensuing parental guilt about transmission also distinguishes disclosing this disease from giving a diagnosis of cancer and other life-threatening pediatric illnesses. Despite the emotion-laden nature of deciding to disclose a child's HIV status, most

parents do eventually disclose the diagnosis to their child, with the mean age at disclosure being approximately 7½ years.[6]

It is also well-known that a child's capacity to trust develops from his or her relationships with the parents. Postponement in disclosure and the fabrications that often accompany delayed disclosure can disturb this trust. Studies show that around thirty-five percent of the caregivers provided deceptive information when disclosing the diagnosis to the child.[2,6] Children sense when something is out of the ordinary and silence and secrecy can deprive them of the opportunity to explore their concerns or fears and to ask relevant questions. When children are not included in this process, they may feel confused, alone, forgotten, or abandoned.[6]

While disclosure is typically a healthy and necessary step in the child's process of understanding and becoming autonomous, it is equally important for health care providers to be aware of circumstances when disclosure is not advisable. A very young child cannot understand the meaning of an HIV diagnosis and should not be expected to comprehend the seriousness of the situation. A parent who is emotionally unstable, experiencing significant anger or guilt about the infection, in a crisis, or unprepared to allow ongoing discussions about the diagnosis to occur should not be encouraged to disclose at that time. Some children, for example, moderately cognitively impaired children, are not able to keep information confidential. In such circumstances, where disclosure of the diagnosis could lead to serious financial, social, societal, or even physical threats to the family, disclosure should be delayed until a time when the family's well-being will not be jeopardized or the child is developmentally capable of keeping the information to him or herself.[6]

Once the decision about whether or not to disclose the HIV/AIDS diagnosis with a child is made, several factors regarding the actual disclosure discussion should be considered. Parents should identify a supportive adult who will be available to assist the children in processing and coping with the information. Support groups, extended family members, close family friends, and social workers are very helpful in this role.[6] An instance in which disclosure involved both the caregiver and the patient's medical team is provided below.

Case Studies

Case 1: Elena*

Elena is a 10-year-old girl with perinatally infected HIV disease. She lives with her mother, Ms Merelo*, a first generation El Salvadoran immigrant. Ms Merelo contracted HIV from a boyfriend who was both physically and verbally abusive, and when she discovered she was pregnant, she ran away to the United States with the help of a brother who had already immigrated. Ms Merelo's experience with violence both at the hand of her ex-boyfriend as well as in her childhood home, in addition to experiences with discrimination due to her immigrant status, has led her to become highly distrustful of others and extremely secretive. Ms Merelo reports having no social supports, but does acknowledge receiving strength from her faith. She appears to have passed on the values of secrecy and isolation to her daughter, whom she does not allow to visit friend's homes or invite other children over to their home. Despite this, Elena is warm and engaging with others, which often serve to hide significant cognitive delays. A recent history of externalizing behavior and frequent lies about her familial and living situation prompted the referral for mental health counseling.

Around the age of 8, Elena began to question her mother about why she needed to take medications. When Elena was 9½ years old, Ms Merelo spoke with Elena's health care team about diagnosis disclosure. When asked how Ms Merelo had responded to Elena's questions so far, she reported that when Elena asked her why she had to take medication, she had said, "so you don't die", and to what she would say if Elena asked her how she got her disease, Ms Merelo stated that she would tell her "from a horrible violent man." It became clear that Ms Merelo's distrust of others and unresolved trauma may prevent adequate disclosure. It was decided that disclosure would occur jointly, with the psychologist and Ms Merelo working very closely together.

Over the course of 2 months, Elena and the psychologist went through the disclosure process very slowly, by reviewing topics related to health, privacy, and social support, and eventually addressing the basics of HIV, including manners of transmission, myths about the disorder, how it affects the body, and the importance of medication. Additionally, the psychologist met with Ms Merelo and conducted interpersonal psychotherapy in order to try to reduce some of Ms Merelo's social isolation. This was deemed important in order for Ms Merelo to be able to support her daughter in the creation and maintenance of friendships. Myths about HIV were also discussed with Ms Merelo. Ms Merelo and the psychologist role-played questions Elena might ask along with developmentally appropriate answers. At the end of the two months, Ms Merelo disclosed the name of the disorder to her daughter, and the manner in which Elena contracted it. At the request of Ms Merelo, the psychologist was present during disclosure, and assisted in answering Elena's questions. Of note, while Elena was able to accept that she had HIV, she vehemently denied that her mother could possibly have it. This speaks of the importance of follow-up care, postdiagnosis disclosure, where assessment of one's understanding, coping, and interpersonal functioning can be routinely assessed.

* Names have been changed for confidentiality purposes

A parent's decision to discuss his or her own HIV status in addition to the child's diagnosis may lead to other important disclosures, many of which may be long-kept family secrets, including the true identity of biological parents, other family members with AIDS, and facts concerning disease transmission.[7] Most parents decide that they want to tell their children in the comfort of their own home, without others present, but a health worker's offer to be present is often appreciated, especially if a parent fears becoming too upset to complete the discussion. Regardless of where the initial disclosure is held, the disclosure process is best conducted in a supportive atmosphere of cooperation between health care professionals and parents.[7] Accurate, simple, developmentally appropriate, yet complete explanations about the virus and medical procedures should be provided, so that the child does not perceive the required treatments as punishment. The child needs to be reassured that he or she did not cause the illness. Parents should be prepared to answer a barrage of questions ranging from the simple and innocent to the accusing, angry, and emotionally upsetting.[6]

Parents may find it helpful to first discuss disclosure with another parent who has already been through the disclosure process successfully. Role-playing can help in identifying particularly challenging questions or rehearsing the answers to more difficult issues that may arise. Anticipating the child's responses along with planning back-up supports will increase the chances of a more positive outcome. Once a diagnosis is disclosed, it remains disclosed forever. Parents should be made aware of all sources of support that are available to the child and the family.[6]

It is necessary to also discuss the nature of postdisclosure reactions. These reactions can range from "no reaction at all" to a delayed reaction or acute anxiety. Psychosomatic complaints, nightmares, emotional lability, anger, and regressive behaviors more appropriate to a younger developmental stage are common, while other children may present with an adult-like acceptance.[8] It may be days or weeks after the initial disclosure before a child has the courage to ask additional questions,[9] therefore, ongoing monitoring of children's behaviors after disclosure is important. Children need to continue sharing their concerns about both the disease itself and its impact on family members. How the child or adolescent initially understands his or her disease will be very different from how they come to terms with their diagnosis after a major infection, a negative disclosure event, or the loss of a friend or family member to AIDS.

Numerous studies have been published examining the effects of disclosure on both the child and family system. Some studies have found children who are able to discuss their illness with adults have fewer behavior problems and have improved social functioning, school performance, and adherence to medications.[9-11] Other studies have shown an increase in behavior problems and stress levels after disclosure.[12] Studies looking at the clinician's perception of the disclosure process reveal positive outcomes associated with disclosure including improved adherence, enhanced support services, open family communication, and better long-term health and emotional well-being. In a cohort of 13 children between the ages of 9-12 years, Bacha, Smith, and Pomeroy (1998) found children who knew their diagnosis had higher self-esteem and were less depressed than children who did not know their diagnosis. Blasini and colleagues reported positive psychosocial adjustment in HIV infected children (N=26) who learned their diagnosis in the context of a supportive environment.[13] Mellins and colleagues (2006) examined a cohort of 77 parent-child dyads with a mean age of 8 years (range 3-13) and 7 as the mean age of disclosure.[14] Thirty percent of the cohort was aware of their diagnosis. The authors noted a trend for less depression among the children who knew their status.

In contrast, New and colleagues found significantly higher scores on CBCL Total and Internalizing Scales and a trend towards higher scores on CBCL Externalizing scale for children (ages 6-12) (N=57) who knew their HIV status versus those who were not yet told.[15] Lester and colleagues (2002) studied 51 families and children (ages 4-13) and found more children in the disclosure group (mean age 10 years 5 months) had been diagnosed with a psychiatric disorder than in the nondisclosure group (mean age 6 years 6 months), but this finding did not meet statistical significance. Increased depression was associated only with more antiretroviral medication doses. Differences in sample size, mode of acquisition, urban versus rural setting, age of child and diverse measures used to assess psychological adjustment may contribute to discrepancy among results.[16] The take-home message from these contrasting studies is that there are likely environmental and contextual variables that influence how disclosure is received, interpreted, and processed.

During adolescence, additional concerns arise. Not only does nondisclosure of HIV status reinforce stigma, foster secrecy, and prevent the individual from assuming responsibility for their own health care and well-being, it also places adolescents who are sexually active at risk for unknowingly exposing others to HIV. For adolescents who are sexually active or considering becoming sexually active, diagnosis disclosure to sexual partners is critical. Most adolescents fear the consequences of disclosure of their diagnosis and therefore wish to avoid such discussions. O'Brien and colleagues (2003) found that the majority of HIV positive young adults disclosed their status to their main partners and family members, but less than one fourth disclosed to any casual sex partner.[17]

In addition, adolescents and young adults often lack the skills and confidence to discuss such sensitive topics with their potential sexual partners. HIV infected adolescents need to know that by engaging in sex, they place their partner(s) at risk of infection and that having sex with someone without informing them of the HIV infection raises enormous moral concerns and can, in some jurisdictions, subject them to potential criminal penalties. They also need to be educated about the use of safe sexual practices, should they choose to have sex. Social support and open communication about the diagnosis are essential, particularly since decisions about relationships, sexual activity, drug use, and plans for the future are the focus of adolescent development and individuation.

Guidelines around disclosure of HIV to children and adolescents can be found at: http://www.hivguidelines.org/GuideLine.aspx? pageID=258& guideLineID=140.

Adherence

Part of the urgency for disclosure in youth is that as children get older, they begin to question the necessity for their medication and health care regimen. This often occurs at a time when they begin to exert more control over personal health decisions. Children naturally strive towards increased autonomy as they enter preadolescence, and family relationships reorganize from a hierarchy of roles to more egalitarian decision-making between the adolescent and the parent.[18] Yet the transition from parent-directed disease management to adolescent-directed disease management is often bumpy along the way, with early adolescence being a time when adherence is often poor. Unfortunately, even minimal nonadherence to protease inhibitor regimens can lead to an increase in an individual's viral load, reduced treatment efficacy, increased risk of contracting opportunistic infections, and an increased chance of developing viral resistance. Adherence can also limit the future options of antiretroviral regimens. Since the late 1990s, only a handful of adherence studies have appeared from pediatric clinical trials groups or from within the adolescent HIV population.[9,17] Adherence rates cited in the literature for adolescents and young adults taking antiretroviral medications ranges from 28.9 to 61 percent.[17,19]

The side effects of the treatment alone often become a significant barrier to adherence to medication and nutrition.[20] As in adults, effective highly active antiretroviral medications can cause diarrhea, nausea, skin rashes and unusual deposits of body fat and lipodystrophy. The process of taking the same medication every day, sometimes several times a day at a specific time can be grueling. Youth often experience conflicts between the need to adhere to a specific plan of care in order to keep their disease in check and other competing demands, such as the need for secrecy about their infection, pressure to keep up with the schedules of their peers, distress around the illness, and the desire to rebel against medical treatment in general.[21] Factors associated with poorer adherence in adolescents include advanced HIV disease, being out of school, higher alcohol use and depression.[6,22] High rates of depression, in particular, raise medical concerns because of the strong relationship between depression and HIV antiviral treatment nonadherence in HIV positive adolescents.[21] A social crisis such as a death, a breakup with a girlfriend or boyfriend, a family fight, or a problem in school or on the job, can also lead to a period of nonadherence. Furthermore, HIV infected teenagers in crisis or teenagers who are depressed may stop taking their medications, no longer eat well, or may be more likely to have unprotected sex.[21] Other factors that contribute to poor adherence include impulsivity, shorter attention spans and a desire to fit in with peers. Oppositional behavior is common and many teenagers are "tired" of obeying parents' and doctors' orders and feel taking their medication is an event that they can control. Teens also express concern that their medications may no longer be effective against the virus and self-discontinue their medications. Teens who are the most adherent are usually well informed about their treatment and feel that taking medications is their own decision.[23]

Cognitive Impairment in Youth with HIV

Children with HIV are at risk for significant cognitive impairment. Manifestations range from mild impairments in certain areas of cognitive functioning to the most severe form, referred to as HIV encephalopathy. Deficits of cognitive functioning associated with HIV status includes slow processing speed, impaired working and long-term memory, poor executive functioning, and poor judgment.[24] Malee et al. (2008) found that IQ scores of children and young adults with HIV tended to fall in the low average range, and that 16 percent of these individuals could be classified as cognitively impaired (FSIQ < 70), as compared to 5 percent in the general population.[25] In addition, for those who are not classified as impaired, subtle neuropsychological deficits may still be prevalent.[26,27] Cognitive impairments not only can have effects on academic functioning, but can also complicate medication adherence, ability to communicate health care needs, and healthy disease-related decision-making.[25] In fact, in a recent study that examined cognitive functioning in a cohort of perinatally HIV infected and perinatally HIV exposed but uninfected adolescents, the HIV infected youth had lower scores of receptive language and word recognition skills. These

findings were not associated with current health status and highlight the importance of educational interventions throughout one's academic life.[28]

On the more severe end of the spectrum, HIV encephalopathy manifests in youth as global and debilitating neurodevelopmental deficits, with the possibility of losing previously acquired skills.[29] The early prevalence of severe HIV encephalopathy, characterized by brain atrophy, motor abnormalities and cognitive delays was estimated to be approximately 13 to 23 percent,[30,31] but has decreased with the introduction of HAART in the US.[32] Neurological changes can impair language, motor, and behavioral functions. When this occurs, children may have problems functioning in school, struggle with social relationships, and consequently have a lower sense of self-competency.

Psychological Symptoms and Psychiatric Disorders in Youth with HIV

Evidence suggests that the majority of HIV infected children ages 6 to 11 are psychologically stable[33,34] despite the stress inherent in living with the disease. With age, however, psychological distress appears to increase on measures of social function, anxiety, depressive symptomatology and conduct problems along with a decline in positive social self-concept.[7,15] A review of reported DSM psychiatric diagnoses in pediatric HIV/AIDS found average prevalence rates of attention deficit hyperactivity disorder at 28.6 percent, anxiety disorders at 24.3 percent, and depression at 25 percent,[34] but the analysis did not distinguish between populations by age or mode of transmission and may have missed important determinants of specific psychopathology. A study by Misdrahi and colleagues (2004) examining psychopathology of HIV infected youth ages 6-15 suggests that depression (47%) and attentional disorders (29%) are the most common psychological comorbidities with HIV disease, and that depression may be associated with encephalopathy and worsening immune function.[33] A small study of HIV+ adolescents with sexually acquired HIV found high rates of mood disorder and substance abuse.[36] A sample of adolescents with perinatally acquired HIV, using the Diagnostic Interview Schedule for Children (DISC-IV), reported higher rates of anxiety and other disorders[14] than had been cited in earlier reports. In a recent study by Wood and colleagues (2009) designed to explore the association between previous severe HIV disease, defined as past CDC class C diagnosis, and neurocognitive and psychiatric outcomes in long-term survivors of perinatally acquired HIV, a distant history of AIDS diagnosis was associated with an increased risk of both neurocognitive and psychiatric impairment (Wood 2009). The authors found 48 percent had a diagnosed psychiatric illness, with 18 percent having multiple psychiatric comorbidities confirming the overall high rates of behavioral disorders, ADHD, and psychiatric[35] hospitalization within the HIV infected adolescent population. Further research is clearly needed to delineate whether early treatment, possibly soon after birth and definitely prior to AIDS diagnosis, might lead to improved CNS outcomes.

Case 2: Jeremy*

Jeremy is an adopted 19-year-old young man with vertically transmitted HIV with a long history of psychiatric treatment. Like many children born early in the US epidemic, his adoptive family had altruistic motives in taking care of what was expected to be a dying child whose parents had already died of HIV and whose siblings were sent to live with other relatives. But, with the introduction of highly active antiretroviral medications, many of these young HIV "hospital boarder babies" survived with complex educational and medical needs. Jeremy was first diagnosed around age 5 years with attention deficit hyperactivity disorder and was treated with multiple stimulant trials. His adoptive mother was frustrated by his hyperactivity but would not participate in behavioral therapy. Jeremy had difficulty in school and had to repeat 3rd grade. Annual neuropsychological testing found him with an average IQ and he was classified as "not apparently affected" with regard to encephalopathy, but continued to need an individualized educational plan to manage his short attention, impulsivity, talking back to authority, and pronounced hyperactivity. He refused to attend regular psychotherapy but had regular psychotropic medication visits with his pediatrician.

Around age 13 years, Jeremy's dog died of cancer and he began to exhibit angry, oppositional behaviors. He reported being depressed and losing interest in activities. He became more withdrawn from his peers and family. He also began experimenting with alcohol, tobacco, and marijuana. He was psychiatrically hospitalized on 3 occasions over the next 2 years and given a diagnosis oppositional defiant disorder, conduct disorder, and major depression. He also met criteria for substance use disorders. He was treated with SSRIs and family therapy with little success. His adoptive mother felt overwhelmed caring for an adolescent with so many psychiatric problems and worried he was a bad influence on the younger children in her home. Jeremy continued to have difficulty remaining on any of his medications including his antiretroviral medications. He was truant from school on many occasions but eventually graduated high school. He is currently living in a group home for troubled youth and young adults and working at a minimum wage job.

* Names changed for confidentiality purposes

As illustrated in this case study, higher rates of psychological disturbances in HIV infected youth, and higher rates of psychotropic medication use and of psychiatric hospitalizations in comparison to HIV uninfected controls[35] have been found. A cross-sectional study at the National Cancer Institute found that over a four-year period, almost half of these youth were prescribed at least one psychotropic medication (often antidepressants or stimulants), a rate much higher than in the general population.[7] A recent study by Ferrando (2009) describes the use of psychotropic medication in patients with HIV as both feasible and effective.[36] For depression and anxiety, extant literature has found that SSRI's show few interactions with antiretroviral medications and a low side-effect profile, and the combination of psychotherapy (either supportive or interpersonal) in conjunction with an SSRI was the most effective treatment for HIV positive adults with comorbid anxiety or depression. Ferrando also examined the cooccurrence of bipolar disorder and HIV. HIV associated mania has been reported to be a secondary affect of HIV infection and has a slightly different presentation with manic HIV positive individuals having greater levels of irritability and cognitive impairment, but less hypertalkativeness. In addition, antiretroviral agents that are able to reach the cerebrospinal fluid are quite effective in reducing symptoms of HIV related mania. The standard medications for mania and Bipolar Disorder, including lithium, valproic acid, or carbamazepine, can be utilized in patients with low viral loads and healthy CD4 counts; however, in individuals with late-stage HIV, these antimanic medications have been reported to stimulate HIV replication and lower serum levels of protease Inhibitors.[38] For HIV induced psychosis, clozapine has been found to be both safe and effective, though not for patients who are taking ritonavir.

HIV associated dementia[37] (HAD), well-described in adults,[39] may rarely also be seen in HIV+ adolescents who become treatment resistant or discontinue treatment. This clinical picture is becoming more common and low dose atypical antipsychotic medications can be useful. Haloperidol and chlorpromazine have been identified as being equally effective in treating dementia, while lorazepam actually worsened symptoms of dementia by exacerbating rates of confusion, ataxia, disinhibition, and sedation.[2] Of note, there is little research on the use of psychopharmacology in adolescents in the general population,[3] much less in adolescents with HIV. Future research on the best treatment approaches of psychopathology in youth with HIV is needed.

Other psychological phenomenon seen in youth with HIV include body dysmorphia and heightened bodily concerns.[40] Clinical reports have identified a growth lag that appears early and persists throughout later childhood with HIV positive boys and girls presenting with short stature and weighing less than their uninfected siblings and peers.[41] Delays in sexual maturation compared to the general adolescent population have also been reported.[42] Delay in pubertal development may impact the psychosocial development of a child and potentially add to social stigma of HIV disease. Like other chronically ill pediatric patients who have diminished skeletal growth and delayed puberty, HIV infected children and adolescents may be more distressed about their actual or perceived pubertal delay than about their underlying chronic illness.

As noted earlier, many of the adolescents living with HIV have already experienced significant hardships prior to their diagnosis including poverty, violence, abandonment, and living environments with constant threats and dangers[42] and experience additional negative life events after learning their diagnosis.[43,44] Regardless of how the teenager acquired his/her infection, the most damaging result is its effect on the formation of relationships outside of the family.[8] These adolescents often fear social rejection more than they fear dying from the disease. Unfortunately, there is a general reluctance for HIV infected youth to seek or utilize mental health services or to attend traditional support groups despite the potential these services have to offer of tremendous benefit. This reluctance may be due to the additional stigma associated with receiving mental health care as well as the fear of disclosure if they were to "meet someone they know".

Loss and Grief

There is a phenomenon known as 'anticipatory grief' that begins at the time of learning one's HIV diagnosis. Feelings of loss of certainty and fears pertaining to the future, relationships, health, control, sexual desirability and body image, accustomed lifestyle, status, dignity, privacy, and security are common. Throughout the course of illness, grief is one of the most frequent and potent life stressors impacting the lives of individuals infected with or affected by HIV.[45] Grief for these individuals differs from grief associated with other chronic illnesses due to exposure to multiple individuals in one's family being HIV infected. These youth may also experience deaths of peers who were HIV infected as well as perhaps a sibling and one or both parents. The social stigma associated with HIV/AIDS can also inhibit successful mourning. This phenomenon is known as disenfranchised grief, or grief that is not or cannot be openly acknowledged.[46]

The loss of one's parent is an all too common phenomena for HIV positive youth. A 2007 study revealed that between 1980 and 1998, 51,473 women with AIDS

died, resulting in 97,376 children without mothers.[47] The death of a parent significantly impacts the surviving family members and leaves a gap caused not only by the lack of the deceased parent's physical presence, but by the part that parent played in framing and directing the family's life.[48] Many family units do not remain intact after the death of a parent. Frequently, parental death disrupts the existing family unit when siblings go to live with various relatives, who may live in other geographic locations. Unfortunately, some siblings lose all contact with one another during this challenging grieving period and are left to cope with parental death in the absence of sibling support.

As many HIV infected youngsters get older, they find themselves thinking about, missing, and beginning to grieve for parents, siblings, and/or close friends who did not live long enough to benefit from currently available drug treatments. Often, it is not until late adolescence that the impact of these losses "hits home." This distress tends to peak at times of transition when other losses are experienced, such as when the older adolescent is required to leave their pediatric care providers and move their care to adult programs or centers.[49] Unresolved and complicated grief reactions can manifest as difficulty making decisions, feeling "lost," guilt surrounding survival, oppositional behavior, depression and anxiety, each of which can lead to disabling mental health problems. Assessing for grief reactions needs to be a part of the mental health assessment and care provided for each HIV infected child, adolescent, and surviving young adult. The case below provides an example of some of the complicated issues concomitant with HIV associated grief.

CASE 3: TASHONA*

Tashona, a 24-year-old young woman, recently requested counseling. She described feelings of "panic" and "uncertainty" and sometimes feeling "so blue, I don't want to talk to anyone". Tashona was born HIV positive. Her biological mother was infected by a boyfriend but did not learn of her infection until Tashona was 2-years-old and diagnosed with *Pneumocystis carinii*. Tashona's father was tested at this time and was HIV negative. Tashona's mom died when she was 7-years-old. Until Tashona was 19, she lived with her father and her 2 older siblings. Although someone in her high school asked if her mom died of HIV, Tashona believed what her father had told her—that her mom died of cancer and the reason she went a few times a year to a clinic and took medicine each day was due to a rare immune deficiency. Tashona's greatest fear is that one day when she went to the doctor, she would be told that the rumor was true; not only did her mom die of AIDS, but that she also had the disease. This fear became a reality during her senior year of high school. Tashona coped by taking college classes and working hard at a job. She had few close friends, and had no significant romantic relationships. She had never disclosed her HIV status to either a friend or boyfriend. At the time that Tashona came in for counseling, she had met a young man she cared deeply for. She had also begun dreaming about her mom and was trying to learn as much as she could about her. In counseling, Tashona was able to recognize that she was approaching the age of her mother at the time of her death and was feeling as if she had not yet done anything in her life that was "meaningful". She also was frightened by the prospect of admitting her diagnosis, not only due to possible rejection, but because this would mean that she was "accepting" that she was a person living with HIV/AIDS. Following several months of counseling, Tashona disclosed her diagnosis to her new boyfriend, began keeping a journal, and volunteering in an HIV/AIDS program. Her feelings of panic and uncertainty diminished though periods of melancholy continue which Tashona associates with "missing the mom I never had the opportunity to really know."

Transition

Transition is a complex process that touches upon all aspects of the adolescent's life.[50-54] There are an estimated 500,000 adolescents with special health care needs who turn 18 each year. For these youth, a sense of urgency exists for the transition to adult-oriented care to be smooth and uninterrupted in order to ensure positive health outcomes.[55] As the pediatric HIV population approaches adulthood, they are faced with the challenges of learning to manage their chronic illness, organize their own health care, fill prescriptions, deal with specialists, negotiate insurance and benefit plans, and adjust to living independently, while also making decisions about initiating sexual relationships.[49] Yet, stigmatizing attitudes by health care providers can hinder the success of transition. A recent study found that health care workers rely on the same stereotypes and misinformation about HIV that are commonplace among the general public.[56]

The factors that create the most significant barriers to successful transition include limited access to health care among chronically ill young adults (even a brief gap in coverage can have significant health consequences for individuals with HIV in terms of drug-resistance and reduced medication effectiveness),[57] poor communication between pediatric and adult providers, and lack of developmental readiness. In most cases, the transition from pediatric to adult care has been guided by age limits rather than the achievement of developmental milestones, with most children transferring to adult care beginning at the age of 18 and completing the transition process by the age of 21.[54] This can result in adolescents

* Names changed for confidentiality purposes

aging out of care prior to being emotionally or cognitively ready. The confluence of general risk due to having a chronic illness coupled with HIV related neurocognitive impairment can result in a cohort of youth who are unprepared to address his or her own health care needs.[58]

In addition to medical management, care for HIV positive youth needs to ensure developmental understanding of risky behaviors and of the behavioral steps required to avoid infecting others. With increased interests in romantic and sexual relationships, youth who are HIV positive will likely need assistance in navigating when and with whom to disclose, and how to approach issues of physical and psychological safety for themselves and their respective partners.[59] In a study examining the sexual knowledge, risk reduction self-efficacy and sexual behavior of HIV positive youth, HIV transmission/safer sex knowledge was found to be low.[60] Adult providers may be accustomed to treating individuals with behaviorally acquired HIV, for whom sexual activity is a routinely discussed topic. While adult providers must deal with issues of partner notification and disclosure with adults, they may be less well versed in broaching this topic or in how to help youth cope with peer pressure. Secondary prevention messages need to be incorporated into all routine medical settings. Finally, hesitance by the parents, adolescents, or the pediatrician to transition out of pediatric care can sabotage a successful transition.[49]

Testing

Thus far in the chapter we have focused on the psychosocial factors of HIV for those individuals who were infected perinatally or via transfusion early in life. Yet there are still a large number of youth contracting HIV through behavioral means. In 2004, 13 percent of the newly diagnosed cases of HIV or AIDS were in youth, with youth defined as individuals between 13-24 years of age.[61] The range of reactions to such a diagnosis varies, with consequent depressive and anxious states being common. Many youth react with rebellion, engaging in increased sexual and substance use risk taking behaviors, in an attempt to deny or "stand up to" the diagnosis.[62] Adherence to antiretroviral medication is particularly problematic during this time, as many individuals will inconsistently adhere to or refute medication until they are able to fully accept their diagnosis.[63] However, overall, knowledge of one's HIV status leads to reduction in high-risk behaviors in youth, though this may not occur immediately.[63]

The reaction to a diagnosis of HIV often follows a pattern, in which the person moves through denial, anger, sadness or depression, and fear and anxiety.

Denial, such as denying the validity of the test, may be adaptive at first, as it allows the person increased time to adjust to the news. Sustained denial is problematic, however, as it is often associated with continuation of risky behavior as well as failure to begin antiretroviral medication.

Another possible reaction is anger. Not knowing how the virus was contracted or from whom, can increase the feelings of anger associated with this process. For youth who contracted the disease from a romantic partner, anger, feelings of betrayal, and confusion are common. The clinician should normalize this response, and allow the youth to express his or her anger while beginning to focus on adaptive ways of learning to live with the virus.

Following denial and anger, some youth express feelings of sadness and depression. This often occurs once the youth has accepted the diagnosis. The youth may experience the cardinal signs of depression, including sleep and appetite disturbances, anhedonia, feelings of worthlessness and guilt, inability to concentrate, psychomotor agitation or retardation, and thoughts of death or suicide. The clinician should try to distinguish between thoughts of death associated with being diagnosed with a serious and life-threatening illness and thoughts of death related to suicide or self-injury.

Finally, many individuals experience fear and anxiety following diagnosis. Fear, both of physical correlates and of the responses of loved ones and friends, is common. Often adolescents and young adults are more frightened by the interpersonal consequences, and fear that their friends will reject them upon hearing the news. While some fear and anxiety should be expected, intense feelings of nervousness or agitation, panic attacks, and intrusive worries that interfere with functioning will likely need to be addressed in a clinical setting with a formal mental health evaluation.

An additional factor to consider in evaluating youth with a new HIV diagnosis is that many of these individuals have pre-existing mental health concerns. Thus it is important in the assessment of these individuals to ask about prior mental health functioning and treatment.

End-of-life Care

Fortunately, in the US, HIV disease is now conceptualized as a chronic illness, with increasing numbers of children surviving well into adolescence and young adulthood years. However, despite these advances, end-of-life issues are sad and unfortunate realities for many adolescents and young adults living with HIV.[64] Around the world, an estimated 330,000 children died of AIDS-related illnesses in 2007; approximately 15 percent of the total deaths due to AIDS that year.[61]

In HIV, end-of-life usually presents as a result of overwhelming opportunistic infections in the face of

severe immunosuppression.[21] Severe wasting, chronic diarrhea, and poor quality of life are also frequent. Meetings with the family to discuss options and to explore palliative or hospice care are often helpful, especially if staff members who have been most intimately involved with the child can be present.[65] Many of the young adults whose disease progresses to AIDS have only recently made the transition from pediatric to adult care. Engaging the support of those health care members that were available during their childhood and early adolescent years can be extremely useful. Most adolescents and young adults want to live as fully a life as they can while they are able and also wish to be involved in the decision making process.[76]

While the nature of this finding is likely culturally determined, existing literature shows that the success of comprehensive care is dependent on open discussions ahead of time that address painful decisions including withdrawal of medications, home versus hospital care, do not resuscitate status, and funeral arrangements.[65] Once these logistics have been discussed, the family can reinvest energy to supporting their child. Open communication, pain control, involvement with friends and family, distractions, and the maintenance of familiar routines all convey a sense of security that is important in supporting the dying child and family.[66] For the adolescent or young adult facing the end-of-life, providing an opportunity to share their intimate views and wishes promotes communication while fostering a sense of dignity and respect.[67] An understanding of the youth's journey through HIV is necessary for the clinician to help them in making personally appropriate end of life decisions.

Case 4: Soledad*

Prior to a scheduled session with Soledad, a 6-year-old girl in an HIV clinic, her mother sat down and described in detail how very tired she was. She has been living with AIDS for several years while her husband, who had been unfaithful and unwittingly transmitted the virus to her, remained relatively asymptomatic. Their older children were born prior to the AIDS epidemic, though this little girl, born in 1988, was born with HIV and was now presenting with frequent infections. When the mom left the room, the social worker asked the child if she would like to write a letter to the virus that was making her mom so tired. She wrote the following:

Dear HIV,

I don't like you. Because of you my mom is sick. That makes me feel sad. Because of you my dad is sick. That makes me feel very sad. Because of you my mom and dad could die. That makes me feel bad and very sad. I would cry and cry and cry. Because of you my sisters and brothers are worried all the time about what is going to happen to our family. That is not good. So, hiv, listen to me. I don't like you at all. Go away! Leave us alone. We just want to live without you.

Over the next two years, psychotherapeutic work with this mom entailed grieving the loss of her health and her anticipated loss of life. She very much wanted to leave something meaningful for her children, so that they could always remember how much she loved them. Together with the social worker, letters were written to each of her children. Mom asked that when she passed, the social worker give the letters to each child. Before her death, mom felt ready to write a letter to her husband, expressing forgiveness for his actions and asking him to be the best father possible to their children. Soledad had a hard time visiting her mother when she entered hospice and struggled with anxiety, guilt and sadness. The day before her mom died, Soledad did ask to visit, and was able to hug and kiss her mom and expressed how much she would miss her.

Soledad's dad's health began to deteriorate following his wife's death. Soledad spent an increasing amount of time with her older sisters, started antiretroviral therapies, and attended school. She remained very close to her dad but due to his increasing fatigue, he was not able to provide much structure or consistent parenting. Psychotherapeutic work with the family involved parenting practices, grief counseling and long-term planning for Soledad.

Early adolescence was difficult for Soledad. At the age of 14, Soledad's father died. She moved with a sibling to another state for a few years and psychotherapeutic work involved establishing new medical care and decisions regarding HIV disclosure to the new school and community. Following her father's death, Soledad began to exhibit early signs of clinical depression, including increasing irritability, anhedonia, and poor appetite. A compromised CNS system or the possibility of encephalopathy were considered, and medically ruled out. Treatment with an SSRI began but noncompliance with this medication and ARV's continued. Treatment for her depression was complicated both by nonadherence and by her refusal to talk to a new mental health professional (she was treated at a hospital far away from her hometown). Her high viral load and disease progression contributed to significant weight loss and fatigue, thus forcing her to face the possibility that she, like her parents, would likely die from this disease. Soledad expressed feeling that while the medication for her depression might be helpful for "feelings that are overwhelming me", she also stated that they could do nothing to get rid of her HIV nor bring back her mother or father. Her intense feelings of hopelessness were marked throughout the course of depression.

Soledad had multiple hospitalizations due to opportunistic infections and wasting. When it became clear that the end of her life was near, therapeutic interventions aimed at easing this process were introduced, including

* Names changed for confidentiality purposes

writing letters to and about her illnesses (both HIV and depression), creating a mock will with her final wishes and words, and by extensive processing of the final days of her mother's life. Soledad wanted to say goodbye to the important people in her life in the same manner as her mother, so that she could draw upon the strength of her mother if things became overwhelming. Soledad succumbed to HIV/AIDS at the age of 16 with her siblings present. She stated that she was no longer depressed and ready to die. Presently, each of the siblings cherish the letters their mother wrote to them. They wish their father was also able to provide such a legacy. Her siblings are involved in community organizations providing advocacy and fundraising work in the global fight against HIV/AIDS. This case illustrates the importance of considering the multiple losses endured by youth infected or affected by HIV, especially in the case of the youth's own end-of-life care. In addition, an emphasis on continuing to follow through with important events and traditions following a parent's death helps create a sense of normalcy along with stability.

Psychosocial Concerns in HIV Affected Populations

Any responsible review of the psychosocial concerns associated with pediatric HIV infection must include a discussion of the uninfected but affected members of the family. The social, psychological, and legal implications for the "well" children in the household are immense. Since many of their parents have likely had a series of pre-existing and long-standing family disruptions prior to the HIV diagnosis, these children suffer from widespread anxieties about future losses, who will care for them if all family members die, and concerns about their own health. It is the pervasive threat of death and fear of being left alone that constitutes chronic trauma for child survivors of HIV infection.[67] With no voice to represent them, these "well" or "affected" children are the silent victims of the HIV/AIDS pandemic.

It is common for some of these youngsters to become "parentified," a term used to describe children who are prematurely forced to take on adult responsibilities and roles before they are emotionally or developmentally able to manage these roles successfully.[68] The greater the severity of their parents' illness, the more likely these children assume inappropriate adult role behaviors. Those who report more parental role behaviors also report more externalizing dysfunctional behaviors including risky sexual behavior, alcohol and marijuana use, and conduct problems.[69] One study found 40 percent of young adolescents (ages 11-15) with an HIV positive parent reported using tobacco, alcohol or drugs. This finding suggests that interventions that promote family functioning and address social influence factors are essential.[70] In a more recent study of HIV infected and exposed youth ages 9-16 and their caregiver, a high percentage of HIV+ and HIV– youths met criteria for a nonsubstance use psychiatric disorder.[71] The most prevalent diagnoses in both groups were anxiety disorders (46% for total sample) that included social phobia, separation anxiety, agoraphobia, generalized anxiety disorder, panic disorder, obsessive- compulsive disorder, and specific phobias. One quarter of the sample met criteria for a behavioral disorder (ADHD, conduct disorders, and oppositional defiant disorders), with ADHD being most prevalent. Psychotherapeutic interventions must be provided for all children in an HIV affected household that includes assessing for parentification, providing respite child and parental care, assisting with permanency planning and building legacies, increasing social support networks, and facilitating ongoing mental health services.[23] Special attention must also be given to the envy and rivalry that might arise when the HIV infected child is receiving special medical care and parental attention.[72]

The process of losing a sibling to AIDS may take place in the context of the illness or following the death of one or both parents. Clearly this may be the harbinger of a still more frightening future,[73] leaving these youth at high risk for psychological distress and posttraumatic symptoms. Survivor guilt, guilt over the reaction to the death, guilt over past feelings about AIDS, and guilt over not being able to comfort their sibling or parents can contribute to anxiety and poor self-esteem. Siblings may initially experience a sense of relief as they may have had a dearth of attention during the sick child's illness, but will often soon feel guilt over this relief. In a study examining the impact of HIV related parental death on 414 adolescents over a period of 6 years,[74] bereaved adolescents had significantly more emotional distress, negative life events, and contact with the criminal justice system than nonbereaved youths. Depressive symptoms, passive problem solving, and sexual risk behaviors increased soon after parental death, as compared with nonbereaved adolescents. After one year subsequent to parental death, these levels were similar to the levels of nonbereaved peers suggesting the importance of early family intervention soon after parental HIV diagnosis, prior to parental death, and sustained over time. Recent work suggests behavioral difficulties in preorphans may begin before mother's death and may emerge more fully after 1-2 years rather than at 6 months.[75]

Globally, more that 14 million children have been orphaned by AIDS,[64] with 320,000 in the US and almost half of orphaned children being between 11 and 17-years-old.[76] Within medical centers and community-based programs, screening and family-based intervention for these siblings is needed. These children must be allowed to grieve, feel appropriate anger for the tragedies in their

life, and find ways of channeling these emotions. Eth and Pynoos (1985) have stressed that traumatized individuals cannot mourn until the traumatic elements of the loss have been resolved. The hallmarks of posttraumatic stress disorder are common in cases of sibling loss from other chronic illnesses. Camps geared for the HIV-affected family members have been helpful for many of these children as they provide the opportunity to share their family's plight and meet others facing similar challenges. Leadership and advocacy skills can also be taught in such settings so that the survivor, if interested, can be trained to be a spokesperson for adolescents at risk for HIV infection.

Summary

Despite the development of highly effective treatments for the disease, pediatric human immunodeficiency virus (HIV) infection continues to affect a substantial number of families both in the United States and worldwide. This chapter reviews the psychosocial functioning of children with HIV, including the direct effects on children's neurocognitive and psychological functioning, social stigma, diagnosis disclosure, adherence, transition to young adulthood, sexual behavior, HIV testing, parental illness and possible death, and the needs of affected family members. Children who are growing up with HIV after the loss of their biological parent(s) need the support and recognition that will facilitate healthy grieving, promote emotional stability, and foster future growth and healing.

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6.3

Professional, Ethical and Legal Issues for the Indian HIV Infected Child

Suganthi Iyer

"No discrimination should be suffered by children on any grounds, including in education, leisure, recreational, sports, and cultural activities because of their HIV/AIDS status. Children have a right to access health and social services on an equitable basis, irrespective of their HIV/AIDS status or that of members of their families."

— UNAIDS, World AIDS Day, 1997

Background

The number of children affected by HIV/AIDS is growing proportionally. In human terms, the HIV/AIDS epidemic poses serious threats to children's welfare at different levels. Unlike other parental diseases, HIV is likely to spread sexually between parents and the child's chances of losing a second parent relatively quickly are far higher. Children and adolescents who are affected by HIV/AIDS face psychosocial distress, discrimination and stigmatization, increased malnutrition, lack of security, lack of parental guidance, loss of access to health care, fewer opportunities for schooling and education, loss of inheritance, homelessness, vagrancy, starvation, crime and exposure to HIV infection and other STIs.

The child's distress is often compounded by discrimination and social exclusion directed at individuals living with HIV and their families. This stigma may translate into denial of access to schooling, health care and inheritance rights. For girl children existing gender inequality exacerbates this discrimination. These problems increase children's vulnerability to HIV infection by rendering them powerless through the circumstances of their lives and depriving them of their rights.

Because HIV/AIDS so often impoverishes and stigmatizes the children it affects, they are at a high-risk of having to eke out livelihoods on the street or in other potentially dangerous situations. In view of the adversity faced by children affected and orphaned by AIDS, it is not surprising that a number of studies have found them to be more malnourished and more likely to suffer from a range of diseases than other orphans or vulnerable children. Children and adolescents are also more vulnerable to contracting HIV than adults for a number of reasons. Much of their vulnerability is a direct result of the circumstances in which they live. Although there are laws that attempt to address many of these situations most of them are inadequate and insensitive to the realities of children and young people.

Who is a Child?

"... a child means every human being below the age of 18 years unless under the law applicable to the child, majority is attained earlier."

In most Indian laws, persons below the age of 18 are referred to as minors. The state provides compulsory education till the age of 14, which coincides with the age at which a person may take up legal employment. The age for sexual consent for women is recognized as 16, except if they are married in which case this age is lowered by a year. In terms of crimes, a child below the age of 7 is deemed to be incapable of committing a crime. For a child between the ages of 7 and 12, no Act is an offence if the child has not attained sufficient maturity of understanding to judge the nature and consequences of her/his conduct on that occasion.

Law must recognize that the participation of young persons, especially adolescents in decisions and interventions that affect them, is integral to the success of any HIV/AIDS intervention and to provide sensitive and appropriate support and treatment to young persons affected by HIV/AIDS. Several laws in other countries do in fact differentiate based on this recognition to clarify at what age a child may consent to or participate in a particular act. In the context of HIV/AIDS, this is particularly important since as discussed below, consent and confidentiality in testing and treatment is a key legal, ethical and human rights issue.

Who is a Child Affected by HIV/AIDS?

Children affected by HIV/AIDS are those having a parent or guardian living with HIV/AIDS, those having lost a parent or guardian to AIDS, those living in households fostering children orphaned by AIDS, or those who are themselves living with HIV/AIDS. AIDS orphans are defined as children below 18 years who have lost one or both their parents to AIDS. The traditional definition of orphans was expanded to address the specific vulnerabilities of children orphaned because of HIV/AIDS and to plan for their care and support.

Children's Rights

Internationally, the rights of children are enshrined in the CRC (Convention on rights of child). Every child has the right to complete and wholesome development and opportunity along with specific rights such as the right to family, education, health services, participation in decision-making, freedom of expression, freedom of association and the right against exploitation, trafficking and torture. Article 19 guarantees protection for all children against all forms of physical or mental violence, injury or abuse, neglect or negligent treatment, maltreatment or exploitation including sexual abuse.

India is one of the few countries whose constitution specifically recognizes the rights of children. Article 15 (3) of the constitution enables the state to make special provisions for children. Article 39 prescribes as a Directive Principle of State Policy that the age of children should not be abused and citizens should not be forced by economic necessity to enter vocations unsuited to their age and strength; that children should be given opportunities and facilities to develop in a healthy manner and in conditions of freedom and dignity; and that childhood and youth shall be protected against exploitation and against moral and material abandonment. In the context of HIV/AIDS these provisions mandate the state to reduce the vulnerability of children through legal and policy protections and by providing state support for well-defined and well-targeted services.

Basic Ethical and Legal Issues

National laws[1] and policies have adopted antidiscrimination, consent and confidentiality provisions.

Consent for Testing and Treatment

As HIV infection rates increase, the issue of consent for and from children for testing and treatment is of much consequence.

This doctrine allows children who show an understanding of the risks and benefits of a proposed treatment or other issues in need of decision-making to make the decisions themselves and "was developed to prevent the usual necessity for parental consent from becoming a barrier to treatment about which children may be reluctant to inform parents".

This rule also empowers minors in nonfamilial settings such as street children to access essential health services.

Informed Consent of HIV testing, treatment and research: What the law says in case of children?

1. No HIV related test or HIV related treatment of a person or HIV related research involving a person, shall be undertaken or performed except with the informed consent of that person or that person's representative in accordance with (2) below.
2. The informed consent of a person's representative shall be taken only in the following circumstances:
   a. Where the person is under the age of 12 years, from that person's parent or legal or de facto guardian, except for HIV related research, where the person is below the age of 16 years, in which case informed consent shall be taken from that person's parent or legal or de factor guardian.
   b. Where the person is between the ages of 12 and 16 years and, in the written assessment of the concerned healthcare provider lacks the capacity to consent, from the person's parent or legal or de facto guardian, except for HIV related research, where the person is between the ages of 16 and 18 years and, in the written assessment of the concerned healthcare provider, lacks the capacity to consent, in which case informed consent shall be taken from that person's parent or legal or de facto guardian.

Confidentiality

The International Guidelines on HIV/AIDS and Human Rights recommend that States "ensure that children and adolescents have adequate access to confidential sexual and reproductive health services, including HIV/AIDS information, counseling, testing and prevention measures such as condoms". Health care workers cannot disclose a minor's positive status or even the fact that she/he came forward for testing without her/his informed consent. Where a child is not of sufficient age or understanding to give this consent only then should the permission of those with parental responsibility be obtained.

One of the key issues in testing and reporting of results is whether or not to involve a youth's parents in the process. Some adolescents may not wish to involve a parent in decisions relating to evaluation or treatment of HIV infection. This reluctance may arise from a desire not to inform family members about HIV status or behaviors that may place the adolescent at risk.

Although it is usually best to involve the family in the health care of adolescents, this is not always the case. Deference to parental wishes to be informed must not interfere with needed evaluation or treatment of adolescents.

Disclosure of information—What the Law Says?

Right to Privacy

Every person has the right to privacy.

Disclosure of Information

1. Notwithstanding anything contained in any law for the time being in force, no person shall be compelled to disclose HIV related information or any other private information concerning themselves except when a court determines by an order that the disclosure of such information is necessary for determination of issues and in the interest of justice in a matter before it.
2. Notwithstanding anything contained in any law for the time being in force, no person shall disclose or be compelled to disclose HIV related information or any other private information of another person, imparted in confidence or in a relationship of a fiduciary nature, except with the informed consent of that person.
3. Informed consent for disclosure of HIV related information or private information is not required in case the disclosure is made:
   a. By a health care provider to another healthcare provider who is involved in the provision of care, treatment or counseling of a person, when such disclosure is necessary to provide care or treatment in the best interest of that person.
   b. By an order of a court when it determines by such order that the disclosure of such information is necessary for the determination of issues and in the interest of justice in a matter before it.
   c. In suits or legal proceedings between persons, where the disclosure of such information is necessary in the initiation of such proceedings or for instructing counsel.
   d. In accordance with Section 13 (Partner Notification).
   e. If it relates to statistical or other information of a person that could not reasonably be expected to lead to the identification of that person.

Partner Notification

A health care provider who is a physician or a counselor, may inform the partner of a person under their direct care of such person's HIV positive status only when:

a. The healthcare provider bona fide and reasonably believes that the partner is at significant risk of transmission of HIV from such person.
b. The HIV positive person has been counseled to inform such partner.
c. The healthcare provider is satisfied that the HIV positive person will not inform such partner.
d. The healthcare provider has informed the HIV positive person of the intention to disclose the HIV positive status to such partner.
e. Such disclosure to the partner is made in person and with appropriate counseling or referrals for counseling.

Exception

The healthcare provider shall not inform a partner, particularly in the case of women, where there is a reasonable apprehension that such information may result in violence, abandonment or actions which may have a severe negative effect on the physical or mental health and safety of the HIV positive person, their children or someone who is close to them.

Discrimination

Children face discrimination in a variety of settings. Denial of health care, inheritance rights, sexual health information, denial of education, isolation in children's/correctional homes, all discriminate against children and lead to severe impediment of their rights. Children face discrimination on the basis of their own HIV positive status or even on the basis of having a parent with HIV/AIDS or in the manner in they can access services and sexual health information.

What the Law Says

Discrimination includes any Act or omission including a policy, law, rule, practice, custom, tradition, usage, condition or situation which directly or indirectly, expressly or by effect, immediately or over a period of time:

i. Imposes burdens, obligations, liabilities, disabilities or disadvantages.
ii. Denies or withholds benefits, opportunities or advantages.
iii. Compels or forces the adoption of a particular course of action by, any person or category of persons, based solely on one or more HIV related grounds.

Explanation

HIV related grounds are:

i. HIV status, actual or perceived.
ii. Actual or perceived association with an HIV positive person.
iii. Actual or perceived risk of exposure to HIV infection.

iv. Any other ground where discrimination based on that ground (1) causes or perpetuates or has a tendency to perpetuate systemic disadvantage in respect of a category of persons, (2) undermines human dignity or (3) adversely affects the equal enjoyment of a protected person's right and freedoms in relation to HIV/AIDS.

Prohibition of Discrimination

1. No person shall be subject to discrimination in any form by the State or any other person in relation to any sphere of public activity including:
   a. Denial of, or termination from, employment or occupation unless in the case of termination:
      i. A person, who is otherwise qualified, in the written assessment of an independent healthcare provider qualified to make such an assessment, poses significant risk of transmission of HIV to other persons in the workplace, or is unfit to fulfil the duties of the job.
      ii. The employer is unable to provide reasonable accommodation due to undue administrative or financial hardship and the employer shall along with the letter of dismissal provide a written statement to such person stating the nature and extent of such hardship. Provided that if the employer fails to provide such written statement, if shall, be presumed that there is no such undue administrative or financial hardship.
   b. Unfair treatment in, or in relation to, employment or occupation.
   c. Denial or discontinuation of, or unfair treatment in, healthcare services.
   d. Denial or discontinuation of, or unfair treatment in, education services.
   e. Denial or discontinuation of, or unfair treatment with regard to, access to, or provision or enjoyment or use of any goods, accommodation, service, facility, benefit, privilege or opportunity dedicated to the use of the general public or customarily available to the public, whether or not for a fee including shops, public restaurants, hotels and places of public entertainment or the use of wells, tanks, bathing ghats, roads, burial ground or funeral ceremonies and places of public resort.
   f. Denial of, or unfair treatment with regard to, the right of movement.
   g. Denial or discontinuation of, or unfair treatment with regard to, the right to reside, purchase, rent, or otherwise occupy, any property.
   h. Denial of or unfair treatment in the opportunity to stand for or hold public or private office.
   i. Denial of access to, removal from, or unfair treatment in, a State or private institution in whose care or custody a person may be.
   j. Denial of, or unfair treatment in, the provision of insurance unless such unfair treatment is based on and supported by actuarial studies.
   k. Isolation or segregation of a protected person.
   l. HIV testing as a pre-requisite, for obtaining employment, or accessing healthcare services or education or, for the continuation of the same or, for accessing or using any other service or facility.

Explanation

1. Without prejudice to the generality of the provision of this Act, Schedule I to this Act is intended to illustrate and emphasise some instances of unfair treatment, which are discriminatory, in order to address and eliminate such treatment and assist persons in interpreting their experiences and treatment.
2. Nothing in this Act shall prevent the state or any other person from taking measures for the protection, benefit or advancement of protected persons including the greater involvement of HIV positive persons.

Children in Families

For children who have shelter and food and live with one or both of their parents, vulnerability to HIV infection is enhanced by sexual activity in the absence of safe sex information, child sexual abuse, drug use, discrimination on the basis of sexual practices, violence, child marriage, and other gender-biased cultural practices. Personal laws and state inaction that indirectly permit child marriages leave young girls in particular vulnerable to HIV.

Laws relating to adoption are unclear on HIV parents giving their children in adoption and the adoption of children affected by HIV/AIDS. These laws also do not address issues of HIV parents' right to adopt.

Another emerging issue is that of inheritance and property right. HIV/AIDS affected children in India are highly disadvantaged in safeguarding their inheritance rights when both parents are dead, "When talking of the legal system, the question is who will administer the estate of a child and too often the answer is the same person who wants to do the grabbing of their property". Legal procedures provide little protection for children's interests with respect to inheritance. A careful assessment of personal and other laws that affect children in families is required to ensure that children affected by HIV/AIDS do not find themselves destitute or without support.

Children in Schools

Children living with or affected by HIV/AIDS in India are commonly discriminated against in schools. In many cases, schools refuse to accept children as students because they are HIV positive or if their parents are HIV positive. Where the child has already been studying in the school and is subsequently affected by HIV/AIDS, school systems often fail to provide a supportive environment to assist the child in coping with the trauma associated with HIV infection.

Two young children in Kerala living with HIV/AIDS were forced to change their school repeatedly because of their HIV status. Parents opposed the inclusion of the two HIV positive children in schools in which their children were studying. Sensitization efforts of school authorities were half-hearted and they completely failed to take a strong stand on the inclusion of the two children in their schools. The children's grandfather was forced to go on a hunger strike before the government paid attention to their plight. After a sustained media campaign, the government decided that the children would be tutored at home, excluding them from the benefits of care, attention, and social connections that families communities and the society of other children can provide, Such a decision only reinforced the children's sense of isolation and failed to protect their equality rights.

Also, in Hyderabad, three HIV positive siblings were denied admission by schools since the management of the schools were against accepting HIV positive children. These schools disregarded the order of the Andra Pradesh government that educational institutions should not discriminate against any one and must admit HIV positive children.

Internationally, courts have clearly established that children affected by HIV/AIDS should not be discriminated against in educational settings and research proved that there was minimal or no societal risk of transmitting the disease to other children.

Children and Health Care

An adolescent who is turned away or whose reproductive health information is not held in confidence is likely to end up with an unplanned pregnancy, STIs or ostracism from parents or the community. Many healthcare providers in India do not see adolescents as having the same rights as adults, and may be reluctant to serve them without parental consent. Healthcare providers deny services to adolescents or fail to respect confidentiality as they worry that making contraceptive methods freely available to adolescents will encourage them to be sexually active.

In other countries children are not only empowered to access HIV testing but can access specific types of health services independently which have been recognized to also have an impact on HIV prevention.

Children and the Right to Education and Information

Sexual health education and information, therefore, can play an important role in providing information to young people about the nature of the HIV epidemic and specific actions they can take to protect themselves from contracting virus.

Denial of sexual health information or the abstinence —only approach to sexuality education interferes with fundamental rights, including the right to "seek, receive and impart information and ideas of all kinds" and the right to the highest attainable standard of health, which can have dire consequences on the right to life.

Further, HIV/AIDS and sex education that addresses the sensitivities of lesbian, gay and bisexual youth has been associated with a reduction in high-risk sexual behavior. However, an impediment in imparting sex education that addresses lesbian and gay youth is Section 377 of the IPC. Any sexual health information that depicts nonpenile-vaginal sex could be seen as abetting the crime punishable under Indian law.

Sexual health information is key to the right to life. The failure to provide accurate information about prevention of HIV transmission puts children at risk of HIV. However, this important right is restricted by obscenity and censorship laws in India, often justified under Article 19 (2) restrictions of the constitution on ground of preserving public decency and morality.

Children and Social Security

Social Security can be understood to be the provision of benefits to households through public or collective arrangements to protect against low or declining standards of living arising from a number of basic risks and needs. In India, incredibly, it is estimated that 90 percent of the working population has no social security coverage for health, death, accidents, unemployment or old age.

Children are vulnerable to exploitation and are often forced into working, being abandoned or tragically allowed to die without treatment. Therefore, social security for health and death that provide benefits and treatment to the affected families are required to prevent destitution that forces children into child labor and living on the streets.

Social security schemes must be varied to meet the different needs and social set-ups that the HIV/AIDS epidemic has created.

Children at Work

The HIV epidemic is likely to increase the number of working children and their working conditions in turn leave them vulnerable to HIV. "The nexus between child labor and HIV/AIDS results from the cumulative effect of three other factors: The inequalities that contribute to and sustain poverty, the failure of prevailing development paradigms to address fully the socioeconomic needs of all people, and the rapid expansion of corporate influence on economic models." Children with parents living with HIV/AIDS or orphaned by the epidemic will, to begin with, drop out of school and/or take up small jobs to supplement the family income. They are exposed to sexual abuse or engage in sex as a survival strategy. Sending children out to be domestic workers is a common survival strategy for poor families. Lack of legal protection of domestic workers makes them especially vulnerable to sexual and physical abuse by their employees, putting them at risk of HIV/AIDS.

In the HIV/AIDS context, the state must ensure that working children have access to education, health, safe working conditions and social security and should accordingly regulate the organized and the unorganized sectors. Working children also miss out on messages from school-based sexual health and HIV/AIDS prevention programs. State education programs should be flexible so as to reach children who work through night schooling at work places with the obligation on the employer to ensure education.

Children on the Streets

For children living on the streets vulnerability to HIV infection increases due to exposure to hazardous labor, sex work, lack of consistent food and shelter and lack of security. Prevalence of sexual activity amongst children living on the street, whether amongst peers or with adults and whether consensual or otherwise is a widely observed reality. Injecting drug use is also common amongst adolescents on the street in many parts of the country. Apart from behavior that could put them at a risk of HIV transmission, the low nutritional levels and health status of street children makes the impact of infection more severe.

What the Law Says

Children

1. The state shall ensure access to child-friendly information about preventive and health-promoting behavior and support to families and communities in implementing these practices.
2. The state shall adopt effective and appropriate measures to abolish harmful practices affecting the health of children, particularly girls, including early marriage, preferential feeding and care of male children.
3. The state shall provide a safe and supportive environment for young persons, that ensures the opportunity to participate in decisions affecting their health, to build life-skills, to acquire appropriate information, to receive counseling and to negotiate the health-behavior choices they make.
4. The state shall ensure the development of youth-friendly health care, which respects confidentiality and privacy and includes appropriate sexual and reproductive health services.
5. In all policies and programs aimed at guaranteeing the right to health of children and young persons their best interests shall be a primary consideration and in the formulation of such policies and programs, the state shall consult children and NGOs working with children at national, state and local levels.

Children Affected by HIV/AIDS

1. The appropriate government shall, in consultation with health professionals and organizations working with children affected by HIV/AIDS formulate guidelines and train healthcare providers on various aspects of care, support and treatment of children affected by HIV/AIDS, including in relation to psychological care and HIV related treatment.
2. The appropriate government shall ensure that children affected by HIV/AIDS can access educational institution and shall formulate and implement programs to address barriers to education including school fees and other costs.

Protection of Property of Children Affected by HIV/AIDS

1. The state shall protect the property of children affected by HIV/AIDS.
2. The state shall, within 90 days of the commencement of this Act, frame rules for the protection of property of children affected by HIV/AIDS.
3. Parents or guardians of children affected by HIV/AIDS, or any person acting in their best interest, or a child affected by HIV/AIDS, may approach the Child Welfare Committee for the safe keeping and deposit of documents related to the property rights of such child or to make complaints relating to the threat of such child being dispossessed, actual dispossession or trespass into such child's house even in the absence of documents related to the property rights of such child.

4. The Child Welfare Committee shall properly maintain and protect all such documents and shall ensure the maintenance of confidentiality of all protected persons.
5. The Child Welfare Committee shall pass appropriate orders in the best interests of children affected by HIV/AIDS, including orders to preserve the property of such children, to make investments of the property or to take possession of documents related to the property where both the parents or legal guardian of such children have either died or are incapacitated.
6. The Child Welfare Committee shall take the assistance of different stakeholders including HIV positive persons, persons working in the field of HIV/AIDS and child-line organization in such matters.

Explanation

"Child Welfare Committee" means a committee set up under the Juvenile Justice (Care and Protection of Children) Act, 2000.

Recognition of Guardianship of Older Sibling

Notwithstanding anything contained in any law for the time being in force, a person below the age of 18 years who is the managing member of a family affected by HIV/AIDS shall be competent to act as guardian of any other persons below the age of 18 years who are members of such family for the purposes:

a. Admission to educational institutions.
b. Care and protection.
c. Treatment.
d. Operating bank accounts.
e. Managing property.
f. For all other purposes that may be required to discharge duties as a guardian.

Explanation

For the purposes of this section, a family affected by HIV/AIDS, is one where both parents or the legal guardian is incapacitated due to HIV related illness or AIDS, those living in households of children orphaned by AIDS or if they are not orphaned, then the legal guardian or parents are unable to discharge their duties in relation to such children.

De Facto Guardian

1. Notwithstanding anything contained in any law for the time being in force, a person who has no parental responsibilities and rights in respect of a child but who voluntarily cares for the child either indefinitely, temporarily or partially, including a caregiver who otherwise has no parental responsibilities and rights in respect of a child, shall, while the child is in that person' s care, have the duty to:
   a. Safeguard the child's health, well-being and development.
   b. Protect the child from maltreatment, abuse, neglect, degradation, discrimination, exploitation and any other physical or mental harm or hazards.
2. A person referred to in subsection (1) may exercise parental responsibilities and rights reasonably necessary to comply with subsection (1), including the right to consent to HIV/AIDS related treatment of, or other healthcare service for, the child if such consent cannot reasonably be obtained from the parent or primary caregiver of the child or the concerned child.

Living Wills, Stand by Guardianship and Testamentary Guardianship

1. Notwithstanding anything contained in any law for the time being in force, a parent or legal guardian of a child affected by HIV/AIDS may appoint, by making a will, an adult person who is a relative or friend, or a person below the age of 18 years who is the managing member of the family affected by HIV/AIDS to act as legal guardian immediately upon the parent or legal guardian's incapacity or death.
2. Nothing in this section shall divest a parent or legal guardian or their rights, and the guardianship referred to in subsection (1) shall cease to operate upon the parent or legal guardian regaining capacity.
3. Parent or legal guardian of children affected by HIV/AIDS may make a will appointing a guardian for care and protection of such children and for the property that such children would inherit or which is bequeathed through the will as per schedule 4 of the Act.

Landmark and Relevant Judgments

X vs Z I [(2003) CPJ 14 (SC)]

Right to Confidentiality: A Supreme Court Judgment

Right to confidentiality is one of the essential rights of a patient. However, there are certain exceptions to this rule wherein confidentiality can be overriden and disclosure permitted. Cited below is a Supreme Court ruling on this important aspect (Decided on 10/12/2002).

The appellant after obtaining the Degree of MBBS in 1987 from Jawaharlal Institute of Postgraduate Medical Education and Research, Chandigarh and MD Pharmacology Course was in the Nagaland State Service as Assistant Surgeon. One Itokhu Yepthomi who was ailing from a disease which was provisionally diagnosed as Aortic Aneurysm was advised to go to the 'Z' Hospital at Madras and the appellant was directed by the Government of

Nagaland to accompany the said patient to Madras for treatment. The appellant was asked to donate blood for the latter. In August 1995 the appellant proposed marriage to one Ms 'Y' which was accepted. But the marriage was called off on the ground of blood test conducted at the "Z" hospital at Madras where several tests were conducted and he was found to be HIV (+). Since the marriage had been settled but was subsequently called off, several people including members of the appellant's family and persons belonging to his community became aware of the appellant's HIV (+) status. This resulted in severe criticism of the appellant and he was ostracized by the community. The appellant then approached the National Consumer Disputes Redressal Commission for damage against the "Z" Hospital, on the ground that the information which was required to be kept secret under Medical Ethics was disclosed illegally and, therefore, the Hospital "Z" were liable to pay damages. The Commission dismissed the Petition as also the application for interim relief summarily by order dated 3rd July, 1998 on the ground that the appellant may seek his remedy in the civil court.

Learned counsel for the appellant has vehemently contended that the principle of "duty of care" as applicable to persons in medical profession, includes the duty to maintain confidentiality and since this duty was violated by the Hospital "Z", they are liable in damages to the appellant. Duty to maintain confidentiality has its origin in the Hippocratic oath, which is an ethical code. The Hippocratic Oath which is reproduced below says: Whatever, in connection with my professional practice, or not in connection with it, I see or hear, in the life of men, which ought not to be spoken of abored, I will not divulge, as reckoning this all such should be kept secret." The International Code of Medical Ethics[2] has also laid down as under: "A physician shall preserve absolute confidentiality on all he knows about his patient even after his patient had died".

The Code of Medical Ethics has been made by the Indian Medical Council provides as under: "Do not disclose the secrets of a patient that have been learnt in the exercise of your profession. Those may be disclosed only in a Court of Law under orders of the presiding judge." It is true that in the doctor-patient relationship, the most important aspect is the doctor's duty of maintaining secrecy. A doctor cannot disclose to a person any information regarding his patient which he has gathered in the course of treatment nor can the doctor disclose to anyone else the mode of treatment or the advice given by him to the patient.

It is contended that the doctor's duty to maintain secrecy has a correlative right vested in the patient that whatever has come to the knowledge of the Doctor would not be divulged and it is this right which is being enforced through these proceedings: It is the basic principle of jurisprudence that every right has a co-relative duty and every duty has a co-relative right. But the rule is not absolute. It is subject to certain exceptions in the sense that a person may have a right but there may not be co-relative duty. The instant case, as we shall presently see, falls within the exceptions.

Hippocratic Oath as such is not enforceable in a court of law, as it has no statutory force. Medical information about a person is protected by the Code of Professional Conduct made by the Medical Council of India. The relevant provision of the Code of Medical Ethics contain an exception to the general rule of confidentiality, in as much as it provides that the information may be disclosed in a court of law under the orders of the presiding Judge. This is also the law in England where it is provided that the exceptions to this rule permit disclosure with the consent, or in the best interests, of the patient, in compliance with a court order or other legally enforceable duty and, in very limited circumstances, where the public interest so requires. Circumstances in which the public interest would override the duty of confidentiality could, for example, be the investigations and prosecution of serious crime or where there is an immediate or future (but not a past and remote) health risk to others.

The General Medical Council of Great Britain in its guidance on HIV infection and AIDS has provided as under: Occasionally the doctor may wish to disclose a diagnosis to a third party other than a health care professional. The Council think that the only grounds for this are when there is a serious and identifiable risk to a specific person, who, if not so informed would be exposed to infection ... "A doctor may consider it a duty to ensure that any sexual partner is informed regardless of the patient's own wishes." Thus, the Code of Medical Ethics also carves out an exception to the rule of confidentiality and permits the disclosure in the circumstances enumerated above under which public interest would override the duty of confidentiality, particularly where there is an immediate or future health risk to others.

The arguments of the learned counsel for the appellant, therefore, that Hospital"Z" were under a duty to maintain confidentiality on account of the Code of Medical Ethics formulated by the Indian Medical Council cannot be accepted as the proposed marriage carried with it the health risk to an identifiable person who had to be protected from being infected with the communicable disease from which the appellant suffered. The right to confidentiality, if any, vested in the appellant was not enforceable in the present situation. Learned counsel for the appellant then contended that the appellant was HIV (+) and, therefore, they are liable in damages. Let us examine this contention.

The European Convention on Human Rights which defines this right as follows:

1. Every one has the right to respect for his private and family life, his home and his correspondence.
2. There shall be no interference by a public authority with the exercise of this right except such as is in accordance with the law and is necessary in democratic society in the interests of national security, public safety or the economic well being of the country, for the prevention of disorder or crime, for the protection of health or morals or for the protection or morals or for the protection of the rights and freedoms of others.

Having regard to the fact that the appellant was found to be HIV (+), its disclosure would not be violative of either the rule of confidentiality or the appellant's Right of Privacy as Ms 'Y' with whom the appellant was likely to be married was saved in time by such disclosure, or else, she too would have been infected with the dreadful disease if marriage had taken place and consummated. Ms 'Y' with whom the marriage of the appellant was settled was saved in time by the disclosure of the vital information that the appellant was HIV (+). The disease which is communicable would have been positively communicated to her immediately on the consummation of marriage. As a human being, Ms 'Y' must also enjoy, as she, obviously, is entitled to, all the Human Rights available to any other human being. This is apart from, and, in addition to, the fundamental rights available to her under Article 21, which, as we have seen, guarantees "Right to Life" to every citizen of this country. This right would positively include the right to be told that a person, with whom she was proposed to be married, was the victim of a deadly disease, which was sexually communicable. Since "Right to Life" includes right to lead a healthy life so as to enjoy all faculties of the human body in their prime condition, the respondents, by their disclosure that the appellant was HIV (+), cannot be said to have, in any way, either violated the rule of confidentiality or the right of privacy. Moreover, where there is a clash of two Fundamental Rights, as in the instant case, namely, the appellant's right to privacy as part of right to life and Ms Y's right to lead a healthy life which is her Fundamental Right under Article 21, the Right which would advance the public morality or public interest, would alone be enforced through the process of Court. For the reasons states above, the appeal is without merits and is, consequently, dismissed.

A civic appeal arose out of the order made by the National Consumer Disputes Redressal Commission that the Appellant shoud seek his remedy in the Civil Court, The Supreme Court upheld the observations made by the National Commission that the Appellant's right was not affected in any manner in revealing his HIV positive status to the relatives of his fiancee (DECIDED ON 10/12/2002).

Contamination due to Negligent Blood Transfusion [II (1994) CPJ 544]

Smt Sunita Vasant Heganawar and Ors.—Complainants

vs

Miraj Medical Center —Opposite Party

This complaint was filed by Smt Sunita Vasant Heganawar, her husband Mr Vasant Pandurang Heganawar and daughter Ku Warsha Vasant Heganawar aged six months. It has been alleged that Smt Sunita Heganawar had some cardiac complaint for which she was admitted in the Miraj Medical Center. On 11.6.90, the Complainant No.1 viz. Mrs Sunita was operated upon. It is an allegation that during the operation she was administered blood by the hospital because of which contracted 'AIDS'. It is her contention that the blood which was given by the Blood Bank of the Hospital was contaminated with AIDS virus. She has alleged that not only has she been personally infected by the AIDS virus but her husband has also been infected because of her contact with him by the AIDS disease and her small child born after the operation has also been afflicted with AIDS. For the negligent and deficient service rendered by the hospital, the complainant has demanded compensation of Rs.10 lakhs. She has also stated that she will have to live with the disease in future for indefinite number of years and therefore the opposite party should admini ster complete medical examination and tests every six months to the complainants without charging any fees. She also demanded that whatever medicines are available at present on this disease—'AIDS' as well as, if new medicines come in the market for this disease in future, they should be supplied to the complainant free of charge. The hospital stated that during the operation of Smt Sunita on 11.6.90, which was performed for the correction of atrial septum defect and mitral stenosis, she was administered blood from the Hospital Blood Bank. After the operation, it was found that the blood pressure of the complaint had gone down below the dangerous level and it was necessary to administer more blood. First one unit of blood was administered during the operation. When the blood pressure had gone down below the dangerous level, and it was necessary to administer more blood, two more units of blood which had already been tested for anti-HIV antibodies were administered. According to the hospital, the first three units of blood were tested for anti-HIV antibodies and were not contaminated with HIV virus. However, the grave emergency continued and the patient was required to be given another unit of blood. Had it not been given, considering the state of the health of the complainant,

she would perhaps not have survived. The hospital in this emergency decided to administer one more unit of blood. This blood was given in good faith and bona fide manner to save the life of the patient. The forth unit of blood was later on found to have been contaminated with HIV and was responsible for the complainant becoming infected with HIV. The opposite party had given an assurance that the hospital was prepared to render all necessary and required medical treatment for the treatment to all the complainants at the hospital, as long as it is necessary. They further offered that some suitable employment will be given to the husband of the complainant by the Hospital so that their problem of maintenance could be taken care of. The medical treatment would be offered free.

A perusal of the records of the Miraj Medical Center proves that no consideration was paid by the complainant to the Miraj Medical Center for her medical treatment. On the basis of these facts, it is clear that the complainant is not a consumer and the provisions of the Consumer Protection Act are not attracted and therefore, this complainant was not maintainable.

In view of the offer made by hospital for free treatment to the complainants and the offer of employment to complainant's husband it was accepted by the complainants and in that event the hospital was directed to adhere to its offer, despite the dismissal of the complaint.

Evidence Needed to Prove Negligence (2007)CPJ 228

M Chinnaiyan —Complainant

vs

Sri Gokulam Hospital and Anr —Opposite Parties

The complainant's wife R Lalitha while taking treatment for abdominal pain in the 1st opposite party Sri Gokulam Hospital was advised to undergo hysterectomy. She underwent that operation in December, 1992. According to the complainant his wife was transfused 2 units of blood in the postoperative period in that Hospital. The blood was obtained from the opposite party Queen Mary's Clinical Laboratory. Apart from the uterine problem, the complainant's wife had no other illness. In mid 1994, she developed recurrent loose motion, weight loss, recurrent respiratory infection and difficulty in swallowing. For this a blood test as well as an ELISA Test were done. The ELISA Test done by the 2nd Opposite Party showed that HIV (Human Immunodeficiency Virus) antibodies were present. The virus leads to the disease called "Acquired Immunodeficiency Syndrome (AIDS)". When it was found that the complainant's wife had been infected with the AIDS virus, she was referred to the YRG Center for AIDS Research and Education for confirmation whether she had been infected by a reliable test. This test was done in June, 1994 and it was confirmed that the complainant's wife had been HIV infected. Since then, she was under the care of YRG Center and she was given medical treatment. She later died in the year 1995 due to complication.

The complainant had paid the 2nd opposite party charges for the blood and the 1st opposite party for the charges for their treatment and operation. The hospital who supplied the blood had to ensure that the blood was free from the deadly HIV. The Hospital had not ensured that the blood was transfused free from HIV/AIDS. There was thus gross and patent negligence on the part of the opposite parties in transfusing the blood which had been infected with HIV and that blood caused the death of the complainant's wife. The complainant and his wife had led a clean life and there was absolutely no other reason for getting HIV infection. It is well known that the persons who are infected with HIV develop complications subsequently. The period between the entry of the virus and onset of the disease could be several years depending on several factors.

The points for consideration are whether the opposite parties have committed deficiency in service in not testing the blood before transfusion and whether that blood had contained HIV. If so what reliefs can be granted to the complainant.

In so far as the 1st opposite party Hospital is concerned, though it is alleged in complaint that before transfusion of the blood they ought to have tested it for HIV, and that they did not do and this amounted to deficiency in service on their part. It is also concerned that since the blood had been obtained from the 2nd opposite party Blood Bank which had been approved by the Government, the Hospital is not expected to do the test and hence not negligent.

Even if the blood obtained from the 2nd opposite was transfused to the complainant's wife, there is no reliable evidence or circumstance that would show that blood contained HIV. It is the case of the complainant himself that when the blood was transfused in December 1992, the HIV was detected after a lapse of about 1½ years that was in June 1994. In these circumstances, it cannot be definitely said that only from the blood transfused HIV had been transmitted and not because of any other reason, and in the complaint it is clearly stated that infection of HIV is due to a number of reasons. The complainant has not stated that his blood had been tested before the transfusion of blood of his wife and this also would show that it cannot be said that there was no possibility of transmission of HIV from the complainant sexually.

The complainant was hence dismissed. There was no order as to costs.

Negligence in Render of Service II (2003) CPJ 434

J. Gopal —Complainant

vs

Nagarjuna Blood Bank —Opposite Parties

The complainant's son Master Akshay aged about 11 months was admitted in the opposite party hospital for complaint of loose motions. After treatment he was discharged on 13.8.1997. Again on 31.8.1997 the boy was admitted for complaint of fever and cough. He was under the treatment of DP Madan Mohan Rao of opposite party hospital who diagnosed the disease allergic breathlessness and anemia. Since the boy was anemic the doctor advised blood transfusion and accordingly as per the advise of the said doctor the complainant approached Blood Bank on 1.9.1997 along with donor Mr JNarsing Rao. The blood bank after conducting necessary tests informed that the blood of the donor is suitable to the patient and that the blood was good and accordingly issued a Donor Card wherein it was clearly mentioned that HIV I and II negative. Accordingly, the blood bank collected the blood from the donor, received Rs. 425/- towards charges, packed the blood of the donor and handed over the same to the complainant for transfusion to the patient. The hospital after going through the reports furnished by the blood bank transfused the blood to the complainant's son who was discharged from the hospital on 3.9.1997 after collecting Rs.2,975/- towards hospital bill. However, as there was no improvement in the condition of the boy, Dr PMM Rao advised the complainant to consult Dr PS Murthy of M/s Mahaveer Hospital. The boy was admitted in the said hospital for treatment on 6.10.1997. As blood test was advised by Dr PS Murthy, the complainant got his son's blood examined and was reactive for HIV test. HIV Western Blot Test at Nizam's Institute of Medical Sciences confirmed the same. The blood bank negligently conducted HIV I and II test and gave incorrect report. The hospital without verifying the correctness of the report issued by blood bank transfused the blood to the patient which resulted with the boy contracting most dreaded disease, i.e. for which there is no cure. The complainant and his wife tested 'HIV non reactive' with a view to eliminate the possibility of the child contracting the disease from the parents. From this material it is clear that the child got the virus transmitted through transfusing one unit of blood contracted from J Narsing Rao certified by the blood bank under Donor Card. The donor was also tested on 4.11.1997 at NIMS and the report reveals that HIV I and II (ELISA)—reactive. This supports the view that child contracted the disease after blood transfusion. Hence the Donor contracted Card issued by the blood bank was incorrect. As the Blood Bank has given the Donor Card negligently without examining properly the blood of the donor, there was deficiency in service on the part of the first opposite party. The second opposite party, i.e. Hospital also committed deficiency in service in not verifying the report/Donor Card issued by the blood bank. The complaint was partly allowed with costs as there was deficiency on part of blood bank and compensation awarded to the child.

Retention of Health Records

1. Duration of preservation of medical record.
2. Admissibility of records in electronic form as evidence in a court of law.

Point No. 1

A. As per notification by Medical Council of India, (Section. 1.3.1), medical records are to be maintained for a period of 3 years from the date of commencement of treatment.

Section 1.3.1 also lays down the standard proforma of the same.

Section 1.3.3 shows the standard proforma of medical certificate.

In those cases where **medical records are the subject matter of any litigation**, these records must be preserved indefinitely because the litigation might go right up to the Supreme Court which may take anywhere around the next 20 years.

Before destroying the medical records it is advisable that a Public Notice be put in two newspapers—one in English and the other in the vernacular language of the State, calling upon the public to collect the said records if they so desire, failing which the records would be destroyed. Such a notice goes a long way in protecting the Doctors and Healthcare Institutions, which subsequently will not be in a position to produce the records, which have been destroyed.

B. As per instructions of The Government of Maharashtra as per Civil Medical Code which is in the office of Director-Health Services the period of retention records as under:

a. Individual Inpatient Medical Record} 5 years
b. Individual Outpatient Medical Record} 3 years
c. Admission and Discharge Register
d. OPD Register
e. Birth Register
f. Death Register
} Permanent (c–f)
g. Operation Theater Register } 5 years
h. Medicolegal Case Register } 10 years

C. There is no legislation with respect to duration of preservation of Medical Records in India unlike foreign countries that have Medical Record Act, Data Protection[3] Act, etc. The above are **only guidelines on** which hospitals have to preserve records.

With Respect to Children

The Code of Medical Ethics/Conduct is silent with respect to how the medical records of a pediatric patient be disposed off. In the pediatric group the right to sue accrues upon the child patient when the child becomes a major, i.e 18 years old and as per the law of limitation (consumer law) this right is not extinguished for a further period of two years, i.e. until the child becomes 20 years of age.

Formerly all pediatric case-papers were thus preserved until the child became 20 years of age. But after the amendment to the Code of Medical Ethics/Conduct maintaining pediatric case-papers until the child becomes 20 years of age is not required as the Code is silent on the same. In this situation a Public Notice in the newspapers as mentioned supra goes a long way in protecting the doctor and the health care providing institutions.

Point No.2

A. As per Indian Evidence (Amendment) Act, 2002, Section 65 B permits any information contained in electronic record which is printed on paper, stored, recorded or copied in optical or magnetic media produced by a computer as also a document which shall be **admissible in any proceedings**, without further proof or production of the original of which direct evidence would be admissible.

B. The above is also stated in Schedule II of Information Technology Act, 2000.

It may be noted that the period of limitation for filing a litigation is 3 years in Civil Courts. However, there is a procedure known as condonation of delay wherein litigations even after 3 years may be admitted. Hence, It is recommended that the storage of medical records should be as per Civil Medical Code followed by the government.

Key Messages

- Article 19 guarantees protection for all children against all forms of physical or mental violence, injury or abuse, neglect or negligent treatment, maltreatment or exploitation including sexual abuse. Article 39 prescribes as a Directive Principle of State Policy that the age of children should not be abused and citizens should not be forced by economic necessity to enter vocations unsuited to their age and strength; that children should be given opportunities and facilities to develop in a healthy manner and in conditions of freedom and dignity; and that childhood and youth shall be protected against exploitation and against moral and material abandonment
- No HIV related test or HIV related treatment of a person or HIV related research involving a person, shall be undertaken or performed except with the informed consent of that person or that person's representative
- No person shall be subject to discrimination in any form by the state or any other person in relation to any sphere of public activity including education, employment, health care services and other services available to general public
- Right to confidentiality is one of the essential rights of a patient. However there are certain exceptions to this rule wherein confidentiality can be overriden and disclosure permitted, as in disclosure in a court of Law under orders of the presiding Judge and circumstances in which the public interest would override the duty of confidentiality
- Medical Records may be preserved as per Civil Medical Code.

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6.4

Nursing Issues in Children with HIV

Margaret Clapson, Jackquie Flynn

Introduction

Human Immunodeficiency Virus (HIV) is becoming a significant child health burden in many resource-poor countries. HIV is no longer a new or emerging disease, and poverty remains a major component driving the HIV pandemic. However, HIV does not discriminate or show favoritism, if given the opportunity, it can and will infect anyone. Families have wherever able or through cultural norms taken in children and other dependents left vulnerable by AIDS deaths, illness, household and livelihood changes, and migration. With increasing numbers of parents dying, orphans and vulnerable children infected or affected are left to be brought up by extended family, NGOs, religious organizations or whatever public provision each country has in place.

This chapter will look at the nursing aspects of care provided in hospital to HIV positive children.

Occupational Risks, Attitude, Stigma and Discrimination

The clinical appearance of HIV in children can be very variable, with some children presenting with well recognized severe HIV related symptoms in the first year of life; while others can remain asymptomatic or mildly symptomatic for many years. The course of HIV disease progresses more rapidly in children, and is extremely aggressive if undiagnosed or untreated. Without adequate treatment, care and support, HIV destroys the immune system, weakening the body's defenses making it unable to defend against diseases and opportunistic infections.[1]

There is little written specifically about the nursing care needed for HIV positive children. The basic core principles of nursing care and medical treatment of nearly all infectious diseases (such as pneumonia, diarrheal diseases, cryptosporidium, malaria, tuberculosis, meningitis) will be the same for any child regardless of his/her HIV status. Most infections are caused by the same pathogens, the difference for a child who is immunocompromised is that the infections are often more frequent, more severe and occur repeatedly.[2] However, since some AIDS-defining conditions [Pneumocystis jirovecii (formerly carinii) pneumonia (PCP), Lymphoid interstitial pneumonitis (LIP), Cytomegalovirus and Kaposi sarcoma] do require specific management; this can readily identify the child (and by association, the family) as being HIV positive, thereby increasing the risk that confidentiality on the ward will be breached.

There is NO moral or ethical justification for refusing to provide medical or nursing care for a child just because he/she is HIV positive.

Occupational Exposure Risk of HIV

It is undoubtedly the fear and misunderstanding of acquiring HIV in a health-setting that leads to over precautions when nursing the child, and thereby furthering the stigma and attitudes of contagion. In fact, every patient, be the child or adult who is receiving medical care, regardless of their presumed infection status, should be treated as a potential carrier of Blood Borne Viruses (BBVs).[3]

A survey carried out in Nigeria in 2004 among healthcare professionals identified 3 most important concerns about treating patients with HIV/AIDS, the first with an overwhelming majority (81%) stating it was the fear of becoming contaminated with HIV.[4]

Every health organization, large or small, must have Infection Control Policies that dictate the safe practice expected of staff to prevent exposures to blood. It is both the responsibility of the employer and employee to reduce the risk of these infections by complying with their local standard (universal) infection control precautions.[3]

All staff should be informed and educated about the main routes of HIV transmission and how to prevent occupational acquisition before starting their clinical practice.

An occupational exposure is defined as:

i. Percutaneous exposure is where the skin has been broken by a needle/other sharp object, human scratch or bite.

ii. Mucocutaneous exposure is where the mucous membranes (mouth, nose or eyes), or non-intact skin have been contaminated.[3,5]

While all body fluids are regarded as potentially infected with HIV, blood is the single most important source of transmission of blood-borne pathogens.

Percutaneous exposure injuries carry a risk, especially deep penetrating injuries involving a hollow-bore needle or a device visibly contaminated with blood.

The actual risk of acquiring a blood-borne virus from a percutaneous injury has been identified as:

- 1 in 3 for Hepatitis B Virus
- 1 in 30 for Hepatitis C Virus
- 1 in 300 for HIV

Research into occupational exposure to BBVs has shown that most incidents occurred in the Ward, Theater, Intensive Care Unit and Accident and Emergency. The majority of nursing injuries are sustained whilst recapping needles or clearing clinical waste, and are preventable with adherence to procedures for the safe handling of sharps and the disposal of clinical waste.[3]

Likelihood of injury and ensuing potential risk depends on a number of factors which includes the circumstances of the procedure, patient behavior (e.g. agitated, anxious or frightened), but also the skill and fitness to practice of the healthcare worker.[6]

Factors that increase the risk of occupational HIV transmission are:

- Percutaneous deep injury involving a hollow-bore needle that has been in the vein or artery of a HIV positive patient with a high viral load[3]
- Undiagnosed HIV positive patient or new patient in late stage disease
- HIV positive patient who has failed antiretroviral therapy and has drug resistance.

HIV Post-Exposure Prophylaxis Guidelines (PEP)

Most PEP Guidelines recommend that for 'optimal efficacy', HIV PEP should be started as soon as possible after the incident, ideally within the hour, and antiretroviral drugs taken for one month. The healthcare worker should notify their supervisor or manager immediately, and follow the protocol correctly.[5]

Judicious testing for BBVs from the index patient avoids unnecessary treatment and minimize the anxiety to the healthcare worker involved.[3] However, this should not be carried out by the injured heathcare worker as they are not impartial to the situation, and unless there is routine testing for BBVs of all patients at each admission; informed consent should be obtained before blood testing as a positive diagnosis has long-term health and social consequences for the patient, and will influence further medical treatment and care.

Universal Precautions with Blood and Body Fluids

All healthcare workers should routinely take appropriate precautions to prevent skin and mucous membrane exposure to blood or other body fluids (cerebrospinal fluid, synovial fluid, pleural fluid, peritoneal fluid, and amniotic fluid).

This will necessitate making a realistic risk assessment, and the safety measures employed are for all patients to prevent occupational transmission of blood-borne viruses and spread of infectious pathogens:

1. Apply good basic hygiene practices with regular hand washing, before and after contact with each patient, and before putting on and after removing gloves.
2. Gloves and plastic aprons are worn whenever there is contact with blood, body fluids containing blood, and other body fluids to which universal precautions apply. Change gloves between patients to prevent any cross-infection.[5,6]
3. Wear protective clothing as appropriate (gown or apron) when there is a risk that own clothing could become soiled, again to prevent cross-infection. This includes protection of eyes, mouth and nose from blood and body fluid splashes.[6]
4. Open footwear should not be worn in situations where blood may be spilled, or where sharp instruments or needles are handled.[6]
5. For all clinical procedures cover existing open wounds and all breaks in exposed skin with waterproof dressings. A non-intact skin surface provides a potential route for blood-borne virus transmission.[5,6]
6. Where sharps usage is essential, exercise fastidious care in handling and disposal, following accepted procedures using designated puncture-resistant disposal containers.[3]
7. Clear up spillages of blood and other body fluids promptly and disinfect surfaces.
8. Follow correct methods for sterilization/disinfection of instruments and equipment.
9. Follow approved procedures for safe disposal of contaminated waste.[3,5,6]
10. Special care should be taken of a deceased HIV positive patient's body due to leakage of body fluids. It is safer to assume that all patients are infectious.[5]

Hospital Admissions

All children when admitted to hospital should have a basic admission screen as per their Hospital's Infection Control policy to rule out any preventable microorganism outbreaks such as Methicillin-resistant *Staphylococcus aureus*.

Universal Precautions do not apply to feces, nasal secretions, sputum, sweat, tears, urine, or vomitus unless any contain visible blood.[4] Since HIV is not transmitted by saliva, ward dishes and utensils used by the child can be washed in the usual way: Bottle feeding is to be strongly discouraged; however, where unavoidable, babies bottles should be washed and sterilized also in the normal way.

However, to prevent cross-infection between patients with other infections, nurses usually wear gloves when dealing with bodily secretions. HIV immunocompromised children pose both a risk of having a 'hospital-acquired infection', and of succumbing to any current contagious infection present on the ward.

Minimum nursing standards recommended by the World Health Organization on hospital care for all children where there are limited resources, states the child should be assessed by a nurse every 6 hours (or 2- 3 hours, if acutely ill), and by a doctor at least once a day.[2] Unaccompanied children will necessitate more input to attend to physical and emotional needs; however this does not have to be provided by qualified nurses and can be facilitated by health care assistants or ward volunteers. Acutely ill unaccompanied child should occupy a bed close to the nursing station where observation and assistance is more readily available.[2]

Good nursing practice must ensure that the following are checked frequently on an iil child:

- Body weight
- Temperature, respirations, pulse and blood pressure
- Food and fluid intake
- Frequency and consistency of stool, vomit, frequency and amount of urine passed.

When a child Needs to be Nursed in Isolation

HIV infection itself does not warrant a child to be nursed in isolation. Isolation restrictions or *Barrier nursing* is only required for children with highly contagious diseases (e.g. pulmonary tuberculosis, diphtheria, chickenpox), or vulnerable children who are immunocompromised and need protection from possible ward infections (sometimes referred to as reverse-barrier nursing).

HIV infection is an important risk factor for acquisition of active tuberculosis, including in children. It is now common practice in adult patients who present with tuberculosis to undergo HIV testing. Although the number of children coinfected with tuberculosis is much less than in adults, good clinical practice is to advocate for HIV testing in children when diagnosed with tuberculosis.[7]

Nursing staff looking after these children should also be fully immunized against childhood diseases wherever possible.[2]

Malnutrition

Often something as basic to life as ensuring chronically ill children receive adequate daily food intake is seen as a menial role and left to parents or carers, or conversely so complicated that only a dietician can intervene. This is not so, and nurses are in a strong position to encourage and monitor the nutritional intake and output of a sick child. For children, weight gain and linear growth are important indicators and valued components of a nutritional assessment. Daily dietary intake and feeding history are important aspects of health evaluation and monitoring, and vital in determining whether the nutritional interventions are working.

Initial nutritional treatment of severe malnutrition in children with HIV/AIDS should be the same as for HIV negative children.[2] Infections alter the body's metabolism and increase the body's nutrition and calorific needs, especially in children. Since HIV and malnutrition lower the body's defenses, children with HIV often fail to gain weight and may develop mobility problems, or show delayed mental development.

Health Professional Attitudes to HIV positive Children and their Families

Nurses due to their professional background are well placed to deliver ethical healthcare as they strive to delivery of high quality care with equity in care delivery.[8]

It is a personal as well as professional responsibility for every health professional to examine and confront their own personal beliefs, values and biases, and refrain from judging others who are different or a minority. Several reported surveys on attitudes and practices by healthcare professionals towards HIV has highlighted that many believe patients with HIV/AIDS should be nursed in separate wards, that treatment of opportunistic infections is a waste of precious resources, and some had refused patient's admission to a hospital.[4]

Research has shown that health care professionals who show respect and acceptance of different ways of living, were considered compassionate and approachable for those people who often encountered disapproval, because of illicit drugs, alcohol addictions, prison record, involvement in prostitution, were transgendered, or lived in poverty.[9]

Stigma

All people living with HIV/AIDS can be seen to share a certain kind of social vulnerability due to the stigma that is still attached to HIV infection. HIV related discrimination is often caused by lack of knowledge and irrational fears about the transmissibility of HIV. Healthcare professionals and workers are no exception to this, and many hold preconceived ideas and "myths" about HIV transmission and what type of person is likely to acquire HIV.[10]

An AIDS diagnosis is defined as a positive test for HIV combined with either an opportunistic infection or other rare presentation. However, this stigmatizing term "AIDS" is often used indiscriminately for any illness or infection a HIV positive child may have, and this labeling is unnecessary since HIV is now considered a chronic life-long condition. Information about a child's HIV diagnosis should be limited to the relevant health professional who needs to know for the purpose of caring for the child.

Psychosocial Support

Children living with HIV have many practical and material needs, but equally have social, psychological and emotional needs. The psychosocial aspects of HIV (such as stigma, secrecy and discrimination) present particular complexities which can affect the care given, or sought, for children with HIV.[11]

Child Protection Concerns

Child protection concerns in pediatric HIV have occurred over breastfeeding, refusal to test the baby, non administration or inadequate supervision of medications, or non-attendance of follow-up of healthcare. Raising child protection concerns is never easy; however it is often those caring for the child who first identify these issues, and must act on them rather than remain silent or collude with the family.

The overriding principle for all providing healthcare for HIV positive children should be to do what is in the best interests of the child. Nurses are often in a unique position to be an advocate for the child, both within the family dynamics and with other health professionals.[12]

Conclusion

The nursing care provided for HIV positive children does not differ to that given to any other child who is admitted with an infectious disease. It is the individual health professional's responsibility to take appropriate precautions to prevent occupational transmission of blood-borne viruses and spread of infectious pathogens by complying with their local standard infection control precautions.[3] Again it is important to state that there is NO moral or ethical justification for refusing to provide medical or nursing care for a child just because he/she is HIV positive.

The care of HIV positive children is best done as a multidisciplinary team effort (nurses, doctors, dietitian, psychologist, social worker) and most importantly, the family or relevant caregivers. However, professional boundaries and personal attitudes can present barriers to really effective team working, and these conflicts need to be addressed.[8] Conflict that occurs, as a result of differing ideology amongst professionals on how the healthcare management of HIV positive children should be delivered, needs to be addressed swiftly.[13]

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6.5

Care of an HIV Positive Child in Day-to-Day Life

Margaret Clapson, Jacquie Flynn

Introduction

In addition to medical needs, children living with Human Immunodeficiency Virus (HIV) have equally important emotional, social, practical and cultural needs. Families, friends, caregivers and healthcare workers provide children with the first line of emotional and social support, and they must be treated as a human being rather than as a disease.[1]

In all societies, the family is usually the primary source of protection and support available to children, whilst communities can provide support for families. However, governments and other agencies also have a responsibility to ensure that children and families are provided with appropriate services. A report published in 2009 drew attention to the insufficient level of formal assistance being provided for families and communities on a national level, and the lack of political commitment and resources available internationally.[2]

This chapter will look at the care of the HIV positive child at home, and the importance of normalizing the chronic life-long disease they and their families live with.

Support and Understanding

Most children acquire HIV through vertical transmission from their HIV positive mothers. Many mothers feel enormous guilt, sadness or anger, and can be blamed within the family for the child's diagnosis. There is often a sense of loss of the "idea" of the once healthy child when the child is diagnosed with HIV. HIV counseling should take account of the child as part of a family. This should include the psychological implications of HIV for the child, mother, father and other family members. Counseling should stress that, although cure is currently not possible, there is much that can be done to improve the quality and duration of the child's life. Caring for a chronically sick child can be physically and psychologically exhausting. Some parents may be in denial about the HIV diagnosis, and as a result may not act in the best interests of their child.

HIV is a "family disease", and affected family members often fear disclosure which impacts on their own lives, relationships and ability to cope. The psychosocial aspects of HIV (such as stigma, secrecy and discrimination) present particular complexities.[3]

Stigma stands at the heart of the fight against the global AIDS pandemic. Nothing fuels the continuing spread of HIV more than fear, ignorance and stigma.

While the societal rejection of certain social groups (homosexuals, injecting drug users, sex workers) may predate HIV/AIDS, the disease has in many cases, reinforced this stigma.[4] By blaming certain individuals or groups, society can excuse itself from the responsibility of providing and caring for such populations.

Having family and community support, plus the opportunity to discuss emotions can help, and accessing local support groups is often useful. In order to counter perceptions of isolation, inability to interact with family members or "feeling contagious", it should be carefully explained how HIV is and is not transmitted. Support for the HIV positive child and family needs to be ongoing, as there are times in the child's life when facing challenges can be particularly significant. These can be when starting HIV therapy, or dealing with discrimination, become aware of own HIV status, difficulty adhering to drugs, or cope with end-of-life issues. Children may also face grief and hardship as consequence of one or both of their parents dying from AIDS.[2]

Living Together with HIV

HIV is transmitted through sexual contact, intravenous drug use, infected blood donations and from mother to child during pregnancy, birth and breastfeeding. However, parents or carers may worry and overestimate the perceived risk that their child could infect others.

There are only a few reported cases of HIV transmission between family members in a household setting, however this type of transmission is very, very, rare. These cases have generally involved blood or other body fluids contaminated with blood coming into contact with open sores or fresh cuts.[5]

Scientists agree that HIV dies quite quickly once exposed to the air, making the chance of environmental transmission remote. To obtain data on the survival of HIV, laboratory studies usually use artificially high concentrations of laboratory-grown virus. These studies have shown that exposure to air reduces the quantity of infectious HIV by 90-99 percent within a few hours.[5]

So, transmission of HIV infection during normal daily contact is not possible. Normal casual contact, including kissing and hugging from a HIV positive parent or child, does not pose any danger to family members or friends.[6,1] The challenge is to educate the child's family about HIV/AIDS, including transmission, disease progression, and treatment. All family members, including extended family members involved with the child, must understand how the child's life will be affected on a daily basis. Misconceptions about modes of HIV transmission have to be corrected as these can influence the development of contamination fears. Parents must be given factual information about HIV so as to reduce fears about its spread.[3] Nevertheless, it is important that household members take precautions to prevent the spread of infection.

Prevention of HIV Transmission and Hygiene Rules in Daily Life

Good hygiene procedures will reduce the risk of passing all infections, not just HIV.

Hand Washing

This is an effective way to prevent the spread of any germs. Wash hands thoroughly with soap and water before preparing food, before eating, and after using the toilet.

Gloves

These should be worn during contact with blood or other body fluids such as urine, feces, or vomit that contains visible blood. Surfaces (e.g. floors, sinks, bathtubs) visibly soiled with blood or excreta should be cleaned with a household detergent or disinfectant (freshly prepared solution of one part household bleach with 10 parts cold water will kill HIV and other germs).[5,6]

Personal Hygiene

- Toothbrushes, razors and razor blades should never be shared among household members. These may become stained with blood and spread microorganisms that may cause illnesses. Because infections can start in the mouth, it is also particularly important that all children see a dentist regularly.
- HIV positive family members should ideally have their own thermometer, however if not possible, clean by washing with warm soapy water after each use, soaked in rubbing alcohol for 10 minutes, dry and store.[1,5,6]
- Menstrual sanitary pads need safe disposal, preferably by incineration or sealed in plastic bag before disposal.[5]

Bathrooms and Toilets

Family members cannot contract HIV from the toilet seat, sink, shower, or bathtub. To further protect when cleaning soiled areas wear household gloves or disposable gloves.[6]

Preparing Food

HIV is not spread through food preparation as cooking will kill any germs. Hand washing is important before handling food to prevent spread of other germs. If you cut yourself while preparing food, throw away the food that is contaminated with blood.[5]

Crockery and Cutlery

Wash crockery and cutlery in hot soapy water, no other special precautions are necessary. There is no need to wash separately utensils used by the HIV positive family members, or have separate crockery and cutlery for their sole use.

Garbage Disposal

Normal household waste can be disposed off in the usual way. Any blood stained, urine or fecal matter needs a separate container (plastic bag), from any household member to prevent spread of diseases.

Laundry

Clothing and bedding can safely be washed with other household members items. Laundry that is visibly soiled with blood, urine, stool or vomit should be washed in hot, soapy water. Heavily soiled items should be placed in a plastic bag separate from other household laundry, the contents soaked and washed in detergent.

Pets and Bloodsucking Insects

Household pets are not dangerous provided the animals are healthy and have up-to-date immunization. Whilst they do not transmit HIV, they can pass other diseases, so the HIV positive individual should wear rubber gloves while cleaning litter boxes, fish tanks, or birdcages, and wash his/her hands immediately following removal of gloves. HIV cannot be transmitted though a biting or bloodsucking insect/parasite even if it bites a person with HIV infection.[5]

Socializing

HIV positive persons can maintain a normal social life. No special precautions are required when visiting friends, eating in restaurants or engaging in casual day-to-day contact with others.

Kissing

There has been no evidence of spread of HIV infection through saliva. Closed-mouth kissing is safe. However, the risk of acquiring HIV during open-mouth kissing is dependant on an extremely poor state of oral health (ulcers, bleeding gums, herpes simplex) and the risk is still considered to be very low.[5]

Human Biting

Transmitting HIV in this way is unusual but not impossible. There have only been a couple of documented cases of HIV transmission resulting from biting. In these particular cases, severe tissue tearing and damage were reported in addition to the presence of blood.[5]

Hair Dressing Salons

Like other businesses and organizations, would be subject to the Health and Safety Protocols which would apply to all customers and staff. Otherwise, in the UK there is voluntary registration with the National Hairdresser's Federation and National Support and Training Services for Hairdressers, involving regular inspections with recommendations. Most reputable salons tend to disinfect and store cutting and styling implements in a solution such as Barbicide and may undertake ultraviolet sterilization of brushes. Ear and body piercing salons should also be employing general infection control precautions and should use disposable piercing equipment. Non-disposable equipment should be kept clean and well maintained.[7]

Nursery, Primary or Secondary school

The general health aim of any nursery, playgroup or school is to prevent spread of communicable diseases and promote good infection control practices for the benefit of both staff and children.[8] Under local Health and Safety Legislation, employers are required to ensure that adequate protocols and provision of the correct protective clothing is available for staff.

HIV positive children have the same right of admission to a school, and access to education as all other children. Having an HIV positive child in school poses no risk to staff or pupils. For the majority of families living with HIV, the fear of discrimination makes them decide against informing the school about the child's status.[9]

In the United Kingdom, it is not compulsory for schools to know the HIV status of a pupil; as universal first-aid procedures and standard hygiene control measures should effectively prevent the possibility of non- sexual transmission of HIV.[9]

HIV positive children who are immunocompromised or have a chronic lung condition, are more susceptible and at greater risk from general infections and childhood illnesses (such as measles, chickenpox) than HIV negative children. Many HIV positive children actually die from common childhood illnesses. Some of these deaths are preventable by giving routine scheduled immunizations and improving nutrition.[1]

Good basic hygiene precautions offer sufficient protection; by not following infection control procedures, (which should be in place regardless of HIV), people in general frequently put themselves and others at risk of many kinds of infections. Children's lack of prior exposure to infections and their poor hygienic practices enhance the potential for infection to spread quickly, and young children should be supervised with hand washing.

Examples of Good Practice on Infection Control in Educational Settings[8]

- Procedures in place to record and report to parents/ guardians that there is an infection outbreak, which will enable them to act appropriately
- Guidelines on when to notify parents during school hours if the child is ill or had an accident
- Any child coming from a household where there are recent cases of certain diseases will be required to remain at home during the incubation period[8]
- Any child with episodes of diarrhea and/or vomiting to be excluded for 48 hours
- Hand washing prior to eating or after going to the toilet/ changing nappies will protect both children and staff
- Disposable gloves and aprons clothing should never be used for more than one child and disposed off after each task into a clinical waste bag
- Provide adequate and accessible sinks with clean running water and soap
- Changing mats should be cleaned with hot soapy water and wiped dry after each change
- Blood spillages must be cleaned up immediately using plastic gloves and bleach solution or chlorine granules if available[8]
- Cuts, sores, or breaks should be covered with a waterproof plaster or other suitable dressing.[5,8]

Any child who is biting other children should be strongly discouraged from doing so. Apart from the very low risk of HIV transmission, the risk to an immunocompromised child whose skin is punctured by a bite is of bacterial infection. It is important to check whether anyone who is injured through being bitten or scratched has been immunized against tetanus.[1]

A child with HIV should not be prevented from doing contact sports (except boxing) if they are clinically well, with no health issues concerning platelets and clotting. Universal precautions would again apply for any child sustaining a wound whilst involved in sporting events.[1,6,8]

Self-Esteem and Identity

Play and social contact are a part of keeping generally healthy. Neglecting these due to fear and stigma can cause social isolation, which can be detrimental to self-esteem.[1]

This may result in long-term psychological effects, including poor social and communication skills, an inability to form lasting relationships, a lack of trust in others and feeling "infectious".

Goffman's[10] classic study suggests that stigma is essentially about how individuals and society stigmatize those we perceive to be different to ourselves, and the lengths people go to in order to mask their 'differentness' and pass as normal.

Stigma is therefore a process in which all members of society are implicated, whether it is passive or active participation.[4] So, it is up to each individual to look hard at how we perceive someone with HIV, and treat them as we expect to be treated ourselves.

Confidentiality

There are many kinds of confidential information, and HIV is no different to any other.

Where a boarding school or recreational camp is acting on behalf of the parents, they would have temporary parental responsibility. It would be necessary for them to be aware of the health needs of all children in their care. This would allow appropriate action to be promptly taken in the event of an infection outbreak and ensure that any necessary medications are given as prescribed.

Conway[9] reported many examples of school communities reacting inappropriately to the disclosure of a child's or parent's HIV status, such as pupils being excluded, and confidentiality not being kept. Information about an individual pupil or family HIV status should not normally be added to a pupil's record, or if recorded, the pupil and family must be informed of this, as it can affect future employment opportunities.

Conclusion

As far as day-to-day living is concerned, a child with HIV should not be treated differently to other children. Their own health needs may differ in terms of susceptibility to and severity of illnesses, they still should be afforded the same care and consideration as any other child.

Affected children (not HIV positive) who have family members with HIV are directly influenced by HIV. They may have experienced the death or separation through hospitalization of a parent or sibling, and will also require psychological and practical support.[6] These children too may be adversely affected by associative stigma if their parents are publicly known to be infected with HIV.[3]

Many of the fears experienced by HIV infected parents and their children were based on misconceptions about modes of HIV transmission. Any misinformation should be corrected as soon as possible in order to alleviate unnecessary stress. Health care professionals who treat HIV positive children may be able to offer counseling to allay fears that family members have about household transmission of HIV.[3]

Schools are an important part of a child's life and provide a supportive, caring environment for children.[9] Whether the school is aware of the HIV status, universal infection control measures should be practiced for any child requiring First-aid for an injury where there is bleeding.[8]

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6.6

Orphans of the AIDS Epidemic

SN Mothi

Introduction

The HIV epidemic is sweeping across the globe and leaving in its wake millions of children devastated by the loss of their parents. This situation is further aggravated by social ostracism, elimination from the educational system and an endless fall through the social security network. Worldwide, HIV is leaving children orphaned and vulnerable to every conceivable danger, disease and disaster.

Global Trends

The most affected area is the Sub-Saharan African region where an estimate has been made of a whopping 12.3 million children rendered orphans by the AIDS epidemic. A continued rise is predicted as more people in the child-bearing age succumb to the disease.

Though prior estimates only included children in the age range of 0-15 years, current estimates include children up to the age of 18 years. However, there are broad age categories: 0-5, 6-11 and 12-17 years which facilitate programmatic implementation processes. A UNICEF report on caring practices in 40 countries of Sub-Saharan Africa shows that more than 90 percent of the orphaned children are cared for by extended families.

There is a debate over the terminology to be applied. "AIDS Orphans," "Orphan and Vulnerable Children" or Children Affected by HIV/AIDS are stigmatizing labels. Upon inquiring what they would like to be called, many of the children responded, "Just call us children."

India

It is estimated that in 2007, there were 2.31 million (1.8 – 2.9 million) people living with HIV/AIDS (PLHA) in India with an estimated adult HIV prevalence of 0.34 percent (0.25 – 0.43%). Out of the estimated number of PLHA, 39 percent are females and 3.5 percent are children. Asia tops the list at 87.6 million orphans due to all causes in 2003 and this is double the number of orphans from all causes (43.4 million) in sub-Saharan Africa.

Definition

An Orphan and Vulnerable Child (OVC) is defined as a child 0-17 years old who is either orphaned are made more vulnerable because of HIV/AIDS. An orphan is defined as a child who has lost one or both parents due to HIV/AIDS. A vulnerable child is one who has been made more vulnerable because of any of the following consequences of HIV/AIDS:

- Is HIV positive
- One or both parents are living with HIV/AIDS
- Lives without adequate adult support (e.g. in a house with a chronically ill patient, a household that has experienced a recent death from a chronic illness, a household headed by a grandparent, and/or a household headed by a child)
- Lives outside of family care (e.g. in a residential care home or on the streets)
- Is marginalized, stigmatized or discriminated against.

Impact of Illness

If a parent dies of AIDS, a child is three times more likely to die even though he or she is HIV negative. The child is more likely to succumb to physical ill health through increased opportunistic infections, faster disease progression and malnutrition.

Psychosocial health and support – The child is likely to face anxiety, fear, emotional deprivation, lack of love and care and may have to care for ill parents. Orphan children typically reside with maternal grandparents or may be sent elsewhere to be cared for. They may have to care for sick relatives or resort to paid or unpaid labor to support themselves or others. Many children tend to adopt

harmful behavior like smoking and drinking to handle the excessively stressful life situations in the absence of a behavior-influencing adult in their lives.

Education – Many children orphaned due to HIV/AIDS are poor with no or limited access to education. Many drop out of school to become the primary breadwinner or caregiver. If a child is seropositive, the common refrain is that it is fruitless to educate a child who is expected to expire in the near future. The need arises because the survival age of affected and infected orphans is increasing as a result of improved access to ART.

Nutrition – Malnutrition occurs because of parental illness, physical and psychological ill health, poor knowledge of nutrition and lack of money, land or skills.

Additional nutrition requirements for children living with HIV/AIDS
(Information below is based on WHO Technical Consultation 2003)

10% increase in asymptomatic children
20-30% increase in symptomatic children
50-100% increase in advanced disease

- Energy requirements are likely to increase by 10% to maintain body weight and physical activity in asymptomatic HIV infected adults, and growth in asymptomatic children
- During symptomatic HIV, and subsequently during AIDS, energy requirements increase by approximately 20 to 30% to maintain body weight
- Energy intakes need to be increased by 50 to 100% over normal requirements in children experiencing weight loss.

Exploitation, Family and Social Security, Stigma and Discrimination

Children who are orphaned due to HIV/AIDS fall through the established social security networks. While a child orphaned due to other causes is usually absorbed into the extended family, HIV may create an impenetrable barrier to such facility. The children who lose extended family support are less likely to access health care, are at a higher risk of labor or sexual exploitation and contracting HIV/AIDS if not already seropositive. They lack legal protection and lose their inheritance rights and access to essential services available to other community members. Professional help from doctors, teachers and lawyers may be less forthcoming to a child who does not have a parent or foster care provider.

Impact on extended family – The extended family faces social ostracism for associating with or caring for a seropositive patient. In this situation, the group is compelled to make a moral decision about caring for an orphan who could also be HIV infected. This seriously affects the stability of the extended family in economic, social and physical aspects.

OVC Care Model

In March 2004, the UNAIDS Committee of co-sponsoring organizations endorsed a framework for protection, care and support of OVC living in a world with HIV/AIDS. The framework considers families and communities to be the foundation of an effective response. It advocates that protection, care and support for OVC be integrated with other programs designed to reduce poverty, promote pediatric well-being, and combat HIV/AIDS.

Issues and Challenges

Within the family – There is a need to keep parents alive, functional and mentally competent as it keeps children away from orphanhood. With the growing awareness of HIV/AIDS, the enormous increase in the number of facilities providing care of HIV/AIDS, and the utilization of more effective antiretroviral drugs, parents are much more likely to live longer if they are managed intensively by the health system. It is important for health care providers to remove the tag of "fatal illness" from an HIV infected person, but rather assign it a chronic disease status. For the health care system, the loss of an infected patient may be only a statistic, but to a child it is the difference between a family life and that of an orphan.

Within the community – When a parent dies and the community absorbs and accepts the child, this greatly minimizes harm to the physical, mental and social health of the child. The child grows with people with whom he/she is familiar and who can be trusted. Though the child has no parent, the child can receive a fair share of love and care from different families and individuals in the community.

Institutional care – Institutional care provided in less than ideal circumstances has been the target of much criticism. Care homes may not be accountable to either the legal system or the government, and children, by virtue of being young and under represented group, cannot complain. Examples are quoted of Non-Government Organizations: CCDT, Mumbai, CHES, Chennai and NAZ Foundation, New Delhi, which pioneered care for OVC. The testimony of the children and the visible outcomes of well implemented institutional care should not be ignored. In the current situation, institutional care could offer much needed respite for orphans of the AIDS epidemic. These children have no extended family to negotiate their needs with, may already be in need of shelter, and may perform much better in an environment of discipline and caring as offered by an institution.

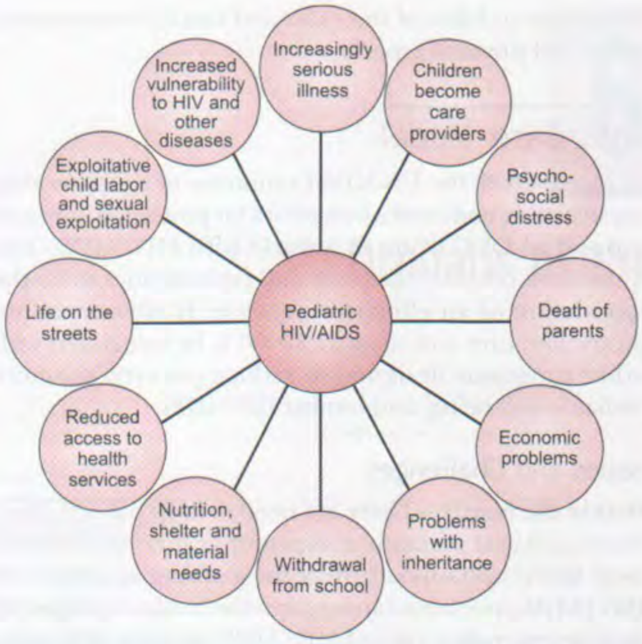


Fig. 6.6.1: Clock of complexities in Pediatric HIV/AIDS—the clock is ticking

Six Core Components have to be Addressed in a Comprehensive OVC Care Model

Food and nutrition – It is important to educate extended family on the safe and hygienic preparation of affordable, nutritional, culturally relevant, socially acceptable, locally available foods. Child care centers or health service providers should be able to assess nutritional status of children (Fig. 6.6.1), identify malnutrition and micronutrient deficiencies at an early stage, and implement and monitor school meal programs.

Shelter – It is important to identify potential caregivers before the parent's death and reintegrate children through family tracing and fostering. The shelter may vary if the OVC is living with parents, extended family or living alone. When a child moves into another home, transition should be facilitated both for the child and the new caretaker. OVC live in fear that they may lose the only other support they have.

Protection – Children should be protected from exploitative, abusive or risky situations. OVC have a right to lead a life free from stigma and discrimination.

Health care – Children born to seropositive mothers need to be referred to a clinical setting for HIV screening, prophylaxis and ART. Children need regular immunization, vitamin supplements and clinical reviews. A child's right to good quality health care should not be compromised.

Psychosocial support – Often parents and extended family tend to protect the child from the true situation and build a wall of ignorance around the child. In a reported instance, a child saw her mother being ill for several days but was never given the reason. Her mother was finally taken away somewhere and the child never saw her again. This leaves a huge void in the child's mind and life. "Will my mother come back? Was I responsible?" These questions, if answered, can help the child to handle huge emotional burdens with strength and dignity. It is important that the psychosocial support is age appropriate. Children less than 5-6 years may not comprehend death and illness. It is also imperative that clear and consistent messages are given throughout the child's life with variations only in the amount of information transmitted and the method of doing so.

Education – A child's right to education must be protected. Children are unable to demand or fight for their own rights, and the responsibility falls on policy makers and implementers. When a child is educated, he/she has a better chance of developing productive life skills and forming good peer relationships and are therefore better able to support themselves and their siblings at a later date.

OVC Care Model to Address Core Components

Role of Health Care Providers

Counselors – Counselors play a key role in the management of children either infected or affected by HIV. They should receive specialized training to effectively guide children. Many times, adult principles are applied to a child with disastrous consequences. A counselor is in the key position of foreseeing a child's possible bereavement, identifying key issues that the child faces or might face, preparing families and children for illness, death and dying, as well as providing palliative and supportive care for those children who are ill themselves.

Social workers and outreach workers – Is there a likelihood of family disputes, violence, alcoholism, sexual abuse or abandonment? The social worker can detect this and can be a powerful voice in the community to create an inclusive and nurturing environment for the vulnerable child.

Clinicians – Children could benefit a great deal by clinicians who change their mindset about the disease and accept it as a chronic disease which requires specific precautions. Similar examples may be recalled of how a concerted effort by the medical profession has almost eradicated leprosy from India.

Role of organizations – Organizations must follow specific protocols as stated in national policy documents or those approved by recognized bodies.

Role of policy makers – It requires a great deal of foresight for a policy maker to understand the consequence of neglecting the needs of this section of society. Children sometimes disappear from statistics, from the public's conscience, and from policy making decisions.

Role of children and adolescents – Children and adolescents are not passive recipients of health services. The practice of involving them in decision-making processes is more likely to ensure that the service provided to them is relevant, accessible and acceptable.

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6.7

Interventions of the NGOs Caring for HIV Infected/ Affected Children in India

Paramita Ghosh, Jayanta Kumar Basu

Introduction

The HIV epidemic in India, first recognized in 1986, is now just under 25 years old and is counted among the most serious public health problems in the country. In 2008, an estimated 2.27 million people between the ages of 15-49 years of India's 1160 million population were living with HIV (PLHIV). India carries the largest burden of HIV behind South Africa and Nigeria. The HIV/AIDS epidemic has increased adult and child mortality rates substantially in many countries including India (NACO 2006). Adult deaths from AIDS often occur among men and women in their thirties and early forties. As a result, many people who die from AIDS leave behind young children as orphans. While in India numerous children are orphaned for a variety of reasons, those who are orphaned by AIDS bear a special burden since they are more likely to lose both their parents. In India, such a development has brought to greater public prominence the problem of 'orphaned and vulnerable children' (OVC). In spite of the fact the problems of orphans and vulnerable children were not well-documented in India, this number of orphan and vulnerable children is expected to double in the next five years (World Bank). Of the 55,764 identified AIDS cases in India, 2,112 are children (Sridhar 2003). It is estimated that 14 percent of the 4.58 million HIV/AIDS cases are children below the age of fourteen years (Sridhar 2003). The National AIDS Control Organization (NACO) estimates show that 70,000 children below the age of fifteen years are infected with HIV in India and 21,000 develop infection every year through mother to child transmission.

UNICEF is the first organization to publish estimates of children orphaned by AIDS epidemic in 1988. *Children and AIDS—an Impending Calamity,* the agency's 1988 study, covered 10 countries in central, eastern and southern Africa. It included the first multi-country estimates of AIDS orphans and the first estimates of the disease's impact on infant and child mortality presented to the international community. In 1997, World AIDS Day release of *Children on the Brink* informed first time the severe effect let it be as it is of AIDS epidemic on children. In 2000, The US Agency for International Development (USAID) estimated that by 2010 that around 44 million children will have lost their one or both parents in 34 countries which are severely affected by AIDS epidemic.

The objective of this chapter is to discuss in detail the major interventions by Indian NGOs for orphans and vulnerable children.

Definition of Orphan and Vulnerable Children in India

In case of India, various institutions, governments and donor agencies have defined OVC differently. According to UN definition orphans and vulnerable children are deprived of their first line of protection – their parents. Overall vulnerable children are defined as those children whose survival and well-being or development is threatened due to the possibility of exposure to HIV/AIDS (Kumar and Schofield, 2008). An 'orphan' is defined as a child under the age of eighteen who has lost one or both parents due to AIDS. Over the time the concept also included the vulnerable children whose survival, well-being, or development is threatened by HIV/AIDS (UNAIDS 2004).

Issues Related to Orphan and Vulnerable Children

As in most cases in India AIDS orphans and vulnerable children stay with the extended families and communities which do not provide them enough for their well-being and growth. As a result in most cases they take up adult responsibilities of generating income and caring for the sick in case they live with their chronically ill parents or family members in poverty stricken household. As a result

they are more likely to be malnourished and have lack of access to basic health and education.

In addition to that is the social stigma and discrimination they face as the child or family member of the HIV infected person. According to the National Human Rights Commission (2005), HIV infected people in India face discrimination from multiple sources including schools, workplaces, medical services, and others, compounding social divisions of class and caste. A study conducted by the International Labor Organization (ILO) found that children of HIV infected parents' experience serious discrimination with 35 percent of them being denied basic amenities and 17 percent forced to take up petty trades to increase their income (Majumdar 2003).

NGO Interventions

Widespread pressure for popular participation and a declining faith in the capacities of governments to solve the problems of social welfare development, led to the global upsurge of organized private activity through a new non-profit sector. The non-profit sector has grown increasingly important in its efforts to provide alleviation of societal problems and injustices and the promotion of democratic values throughout the world in recent years.

According to Brodhead and O'Malley, the term 'non-governmental organizations' applies to diverse organizations that "work together outside of government, to address a need, advance a cause or defend an interest" (Brodhead and O'Malley 1989). However, the World Bank defines NGOs as "private organizations that pursue activities to relieve suffering, promote the interests of the poor, protect the environment or undertake community development" (World Bank 1988; Mercer et al. 1991).

The non-profit sector plays a pivotal role in providing services to children found in need of care in India. The care of OVC is provided almost entirely by nongovernmental organizations (NGOs), which can be divided into formal and informal welfare sectors. The formal welfare sector is long established, has developed infrastructures, employs professional staff and receives government subsidies. Many formal welfare organizations are contracted by government, and receive subsidies, to implement statutory child care provisions. Informal NGOs tend to be more closely aligned with the new developmental approach and rely more on donor funding than government subsidies. Furthermore, many less structured and more indigenous responses to the swelling numbers of children living with HIV/AIDS have evolved in communities, without the support of state subsidies and without being registered as NGOs. These are more difficult to track and to include in any form of classification. The growing number of children in need of care as a result of the HIV/AIDS pandemic has exceeded the capacity of established systems of care.

According to estimates there are around 470 NGOs working with vulnerable children in India and 30 work directly with AIDS orphans (SAATHII 2003). Family Health International in India is working with 22 partners in high-prevalence areas to address the needs of nearly 12,000 OVC. There are organizations in India such as the Naz Foundation and Solidarity and Action Against the HIV Infection in India (SAATHII 2003), Committed Communities Development Trust, Save the Children, World Vision India, Lepra Society, Sai Educational Rural and Urban Development Society (SERUDS), etc. who are doing commendable work for OVC in different parts of India. Some of them work at large level where as others work at small level.

In India NGOs play two broad roles in society that is operational roles and educational and advocacy roles in terms of OVC. Overall there are three broad approaches along which the NGOs involved with OVC in India. They are namely home-based support and care, community based support structure and residential care.

Home-based Care

Home-based care initiatives provide services to households of people living with AIDS, and injuries or other chronic illness. Home-based care models can either have a community base or an institutional base. Community home-based care models recruit community members to visit and care for needy people in their homes. Emphasis is placed on collaborating with community leaders in enlisting community members to be trained as voluntary home-based care workers in order to create a comprehensive, community-owned service. Institutional based care uses experts or professionals from a health care facility to go out into the community to provide care to people in their homes. Most importantly it is very often the home-based care worker who is first on the scene and therefore able to identify vulnerable children before they become destitute.

There is a minimum package of care that is commonly provided by all home-based care initiatives which are as follows:

- Basic nursing care taught to family members equipping them to care for the patient. The patient is also taught how to care for him/herself, adherence to, etc. after ART
- Information on health care and related matters such as good nutrition and preventive measures
- Supportive visit to patient
- Counseling support to caregiver and other family members

- Accompanying patient on visits to hospital or clinic and medical support if needed.
- Provision of food and other material support and educational support for needy families
- Referring to resources in the community

The major challenge of home-based care lies in providing free access to basic social services, psychosocial support and monitoring.

Community-based Support Structure

Organizations in this category offer support to indigenous, informal caregivers. Their focus varies between emotional support, information provision, advice, advocacy, and liaison with income generation activities. Key functions of these organizations, however, are the support they give to caregivers and networking they do with related services and resources. Community based support can be divided into five basic interventions such as:

Community support groups for children and family members who are living with HIV and for uninfected family members and affected others, which can provide:

- Emotional support
- A forum where family members, including children, can discuss concerns and ask questions
- Opportunities for sharing information about available services
- A platform for speakers to discuss prevention, care and treatment
- A focus for educational activities
- A focus for mutual support and income generating projects
- A platform for community advocacy and activism.

Services and assistance to support families affected by HIV/AIDS in ways that enable them to stay together and maintain their home. Such services can be offered by a combination of formal and informal service providers, including government or privately supported agencies, and might include:

- Child or day care
- Health and nutritional support
- Home health care providers
- Income generating projects or direct financial support.

Training for those in the community who interact with HIV/AIDS affected families, can allow more people to contribute to prevention and the provision of quality care, and to offer support to dying parents and their children in planning for the future. Such training can also reduce the fear and discrimination which result from misunderstanding and misinformation.

Peer education programs have been conducted in various parts of the world involving children and adolescents in age-appropriate peer education and education of others in their communities. Children work with facilitators in learning about HIV/AIDS. They design projects, create educational materials, and educate through drama and talks in schools and community meeting places. Such approaches not only provide a mechanism for educating about HIV/AIDS but also encourage confidence and self-esteem in those children and young people who are involved.

Efforts to remove and protect children and adolescents from high risk situations: Such programs or activities need not necessarily be focused primarily on HIV/AIDS but may include activities with children which address their rights and diminish neglect and abuse, through contact with caring adults, access to education, protection, health care and by fostering self-esteem and confidence. These could include:

- Alternative education
- School drop-out prevention
- Tutoring
- After-school drop-in centers
- Skills training for older children (especially those out of school)
- Sports and recreation
- Rescue and recovery for physically and sexually abused children
- Peer drug counseling, education and prevention
- Child care for young parents
- Establishing organizations of children, such as, street children and child laborers.

Residential Care

This is usually the last option for children in need of care, often abandoned or abused children for whom return to community and family of origin is not an option. Traditional children's homes, reform schools and places of safety all fit into this category, all of which have had to consider how they can adapt to the needs of children living with AIDS—whether they are infected themselves or have family members who are infected. Among them there are two kinds of residential care units—temporary shelters and institutions. Under residential care, the NGOs take care of overall development of the children providing education, basic needs, nutritional facilities, medical facilities and other psychosocial support which is necessary for the child.

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Salient Features

- A comprehensive, reliable and up-to-date reference text
- Discusses extensively all the major issues and provides a holistic approach on prevention, care and management of children infected/affected with HIV/AIDS
- Focuses on evidence-based practical information and recent advances in the field
- Emphasizes on prevention with special reference to mother-to-child transmission of HIV/AIDS
- Chapters contributed by the *Who's Who* in the field from across the world
- Useful for hospitals, institutions, governmental and non-governmental organizations involved in caring for children and all practicing physicians, clinicians, pediatricians, obstetricians, family doctors and postgraduate students.



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She has worked with experts from all over the world in the field, many of whom who have contributed excellent chapters in this book. Apart from writing several chapters in reference books on Pediatric and Perinatal HIV, Tuberculosis and Lung Diseases, she has a number of publications and presentations in various national and international conferences and has won many awards and scholarships.



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